Visually Evoked Responses in Man: A Method for Measuring Cerebral Effects of Preanesthetic Medication

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Visual stimulation by a flash of light directed into the eyes appears particularly suitable for studying sensory input in man. The light stimulus is innocuous and controllable. With the aid of electronic averaging devices the visually evoked response (VER) can easily be distinguished from electroencephalographic background activity. In this study the technique was applied to objectively measure cerebral effects of preanesthetic drugs administered to 124 patients scheduled for surgery.

Sedative and tranquilizing agents tended to alter certain components of the VER similar to natural sleep. With the substituted phenothiazines, particularly chlorpromazine, an initial state of turbulence was often observed before the characteristic depression was recorded. Morphine sulfate did not significantly affect the VER. Of the various muscarinic cholingeric blocking agents employed, scopolamine hydrobromide proved to be most effective in altering the VER while its quaternary analogue, methscopolamine, which is known to penetrate the blood-brain barrier with difficulty, had no significant effect.

THE AVAILABILITY of modern electronic averaging techniques for recording sensory responses via scalp electrodes has opened a new, objective approach to the study of pharmacodynamic effects of drugs on the central nervous system. Among the various sensory reactions of interest to the physician, pain certainly is the most important; but since pain areas are not well represented in the cerebral cortex it is difficult to study this reaction using scalp recordings. On the other hand, sensory modalities such as touch, proprioception, and especially vision, are well represented in the human cerebral cortex and can easily be monitored by overlying electrodes. Visual stimulation by a flash of light is especially suitable for studying sensory input in man because such a stimulus is innocuous and can easily be produced and controlled.

As a result of previous studies of the effects of various anesthetic agents on visual input,[1,2] it became apparent that visually evoked responses in man can be altered in various ways, depending on the anesthetic agent used and the degree of anesthesia present. It was found, however, that the response was influenced by the type of preanesthetic medication. These studies indicated that drugs which relieved anxiety, and especially those with hypnotic properties, caused rather dramatic changes in the visually evoked response. Therefore, we have applied the visually evoked response technique to the study of cerebral effects of various drugs used in preanesthetic medication, to determine its usefulness in the objective measurement of the efficacy of these agents to suppress visual sensory input and promote sleep.

Averaging Technique for Visually Evoked Responses

A sensory input, such as light flashed into the eyes, causes a change in the electrical activity of the nervous system which can be amplified and recorded by means of an EEG or other high gain amplifiers, on an oscilloscope or photographic film. The electrical waves obtained are called the visually evoked response (VER). Such a response can be easily identified in an EEG recording from the exposed cerebral cortex. However, using scalp electrodes the VER can only occasionally be distinguished from spontaneous brain

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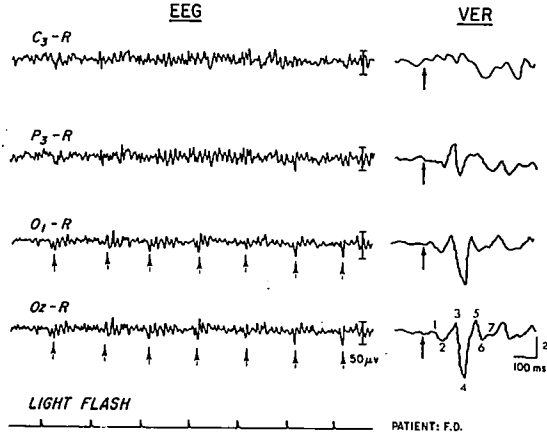

FIG. 2. VER's observed in the spontaneous EEG. The average of 200 evoked responses recorded from the four scalp areas is shown to the right of each EEG tracing. The time of the light flash is indicated below. Note that it is possible to observe an evoked response (arrows) to each light flash although there is considerable variability. The largest potentials of shortest latency are recorded in the occiptal areas (O_1 and O_z). See figure 3 for details of the evoked response.

wave activity in man as shown in the left hand portion of figure 1.

In order to identify the evoked response in the EEG of man, computer techniques must be employed. The computer has to be programmed to initiate the sensory stimulus. All electrical activity resulting from the input stimulus is then electronically added or subtracted until an average of a given number of inputs is obtained. The resultant average can be written out as a permanent record as shown in the right portion of figure 1. It may be noted that the VER obtained in the visual areas of the brain (O_1 and O_z) are of the largest amplitude and have the shortest latency.

Application of Visual Stimulus. A CAT computer was used and set for a 500 millisecond analysis, with an internal trigger for repeating at 1-second intervals. A pulse counter served to stop the light-flashing automatically, after 200 pulsations. An amplified synchronizing pulse at ordinate 20 was used to trigger a Grass stimulator and photic unit set for a flash intensity of 2 and flash duration of 10 microseconds. The strobe light was enclosed in a sound-dampened lucite box to reduce the sound of the lamp click and placed at a distance of 15 cm. from the subject's eyes (fig. 2).

EEG Recording. An Offner Type R 8-channel electroencephalograph was used for amplification and recording. The electrodes (Grass silver-disc type) were placed in accordance with the 10–20 International Electrode System.[3] Bentonite electrode paste with a piece of gauze served to anchor the electrode to the scalp (fig. 2). Electrical potentials were obtained from Fp_1, F_3, C_3, O_1, and O_z to both ears which served as a reference.

The filter settings were placed at high 1 and a time constant of 0.3 seconds for recording the EEG. The output voltage of the 4 channels which recorded C_3, P_3, O_1 and O_z constituted the input of the computer. The analogue output of the computer was recorded as a DC input on one channel of the EEG; 400 milliseconds after the light flash was analyzed. All recordings were made on the left side of the head to both ears which served as the indifferent site. Throughout the entire study, negativity was represented as "up" in the tracings.

An electrocardiographic recording, from lead 2, was obtained at the same time.

Subjects. One hundred and twenty-four patients were selected who were known to be free from neurologic or psychiatric disorders. Both sexes were included and the ages ranged from 2 to 75 years. In each case, the purpose of the study was carefully explained to the patient (or relatives) and permission was ob-

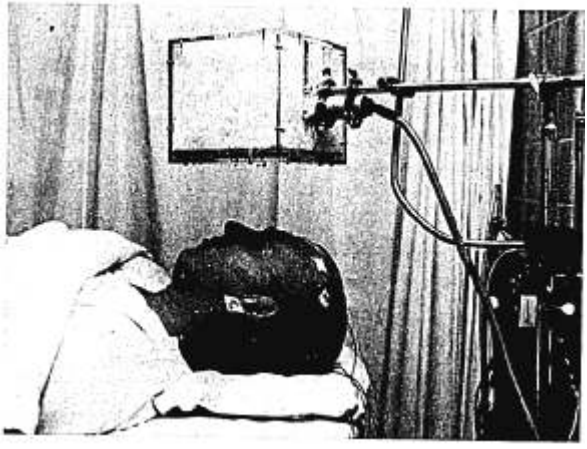

FIG. 2. Placement of the strobe light above the patient's face and position of the EEG electrodes.

tained for carrying out the procedure. No narcotic analgesics or sedatives were administered during a period of at least 12 hours before the VER recordings were made.

Preanesthetic Medication. With the patient resting comfortably in a supine position an intravenous infusion containing 5.0 per cent dextrose in 0.2 per cent saline solution was started, and four sets of the VER (subject's eyes closed) were obtained to establish a baseline reference. Through the intravenous tubing, one of the following medications was then administered over a 30-second period: muscarinic cholinergic blockers such as scopolamine hydrobromide (0.006 mg./kg., 14 subjects; 0.007 mg./kg., 7 subjects), methscopolamine bromide (0.0055 mg./kg., 11 subjects), atropine sulfate (0.0046 mg./kg., 13 subjects; 0.0092 mg./kg., 14 subjects), and *l*-hyoscyamine sulfate (0.00488 mg./kg., 12 subjects; 0.0098 mg./kg., 8 subjects). In addition, the following sedative, tranquilizing, analgesic, or psychomotor stimulant drugs were administered intravenously over a 5-minute period: secobarbital sodium (2.0 mg./kg., 11 subjects), chlordiazepoxide hydrochloride (1.0 mg./kg., 10 subjects), chlorpromazine hydrochloride (0.5 mg./kg., 5 subjects), promethazine hydrochloride (0.5 mg./kg., 6 subjects), morphine sulfate (0.13 mg./kg., 6 subjects), and *d*-amphetamine sulfate (0.05 or 0.1 mg./kg., 7 subjects). Three minutes after the administration of the medication, a series of light-flashes were applied and repeated at about 5-minute intervals. The patient's state of consciousness was determined by his reaction to auditory stimuli and by characteristic changes in the EEG pattern.

Results

Effects of Natural Sleep. Few patients were able to fall into natural sleep without any premedication, before the induction of anesthesia. Some subjects did fall asleep during the control testing procedure, possibly because of the hypnotic effect of the flashing light, but in most cases sleep occurred only when the environment was particularly conducive. During the series of light flashes the EEG was monitored for the presence or absence of alpha rhythm, flattening of the waves, theta or delta waves, and sleep spindles. When sleep spindles were evident and the patient did not respond to a sharp sound, he was considered asleep. Frequently at this stage the patients showed depressed respiration and occasionally temporary obstruction of the upper airway as evidenced by snoring which was easily controlled by supporting the chin. After four to six recordings the patient was awakened and questioned about events im-

mediately preceding as a further check on his state of sleep.

Figure 3 illustrates the characteristic alterations in the VER recorded at the inion to both ears as a reference. This subject showed the typical pattern, as described by Cigánek,[4] of a person who is awake but with his eyes closed. Within 100 milliseconds after the light flash, a primary complex consisting of waves 1, 2 and 3 can be identified; during the next 150 milliseconds a secondary wave complex appears which consists of a predominantly positive or downward deflection. Subsequently, characteristic waves of approximately 100-millisecond intervals are observed which represent the rhythmic afterdischarge, and appear to correspond to the alpha rhythm. It may be noted that waves 1 through 7 and the rhythmic afterdischarge were prevalent initially; as the patient became drowsy the alpha rhythm and the afterdischarge disappeared, and the height of wave 3 was reduced, whereas waves 4 and 6 were still prevalent. With more profound sleep the secondary complex became markedly enhanced, especially in wave 4. When the patient was aroused the VER promptly returned toward the control pattern.

Effects of Sedative Agents. In general, those agents which promoted natural sleep caused a marked diminution in the primary complex, especially wave 3, and enhancement of the secondary complex, especially wave 4. The latency as well as amplitude of these two waves were measured. Table 1 summarizes the data obtained with regard to these components in studies involving secobarbital, chlordiazepoxide, and promethazine.

SECOBARBITAL: In most instances, the administration of secobarbital sodium produced a transient comatose or semicomatose state, from which the patients recovered within 30 to 60 seconds after injection. After being awakened, these patients tended to go back to sleep if left undisturbed, and most could easily be awakened. In several cases, however, the patients were found to be in a coma from which they could not be aroused, within 10 minutes after the administration of secobarbital. Thus, an early stage of coma complicated the picture of natural sleep associated with this drug.

There were marked individual variations in the effects of secobarbital on the VER. As can be seen in table 1, this dose of secobarbital had no significant effect on the latency and amplitude of wave 3 in the primary complex, as evaluated by paired comparison student t test;[6] the tendency for wave 3 to decrease in amplitude was not found to be

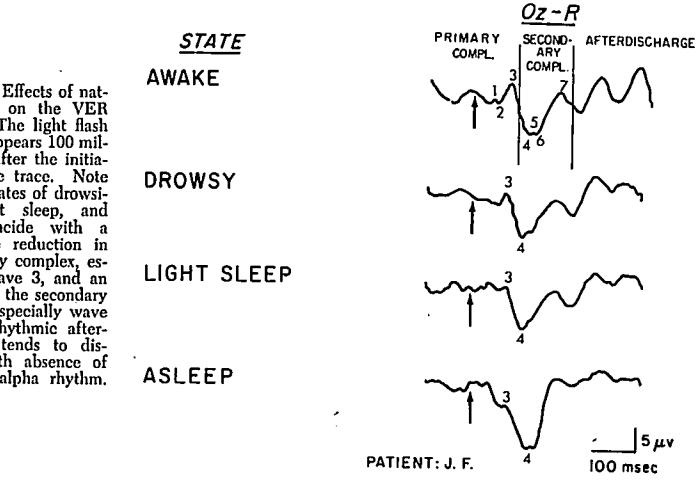

FIG. 3. Effects of natural sleep on the VER in man. The light flash (arrow) appears 100 milliseconds after the initiation of the trace. Note that the states of drowsiness, light sleep, and sleep coincide with a progressive reduction in the primary complex, especially wave 3, and an increase in the secondary complex, especially wave 4. The rhythmic afterdischarge tends to disappear with absence of the EEG alpha rhythm.

TABLE 1. Effects of Various Sedative Agents on Certain Components of the VER

Drug	Dose (mg./kg.)	Wave 3				Wave 4			
		N	Before ± S.E.	After ± S.E.	P Value	N	Before ± S.E.	After ± S.E.	P Value
Secobarbital	2.0	9 11	L 84.19±4.0 A 2.2 ±0.83	L 82.52±4.09 A 1.6 ±0.58	<0.5 <0.4	9 11	L 125.8± 3.9 A 4.15± 1.18	L 126.74±2.9 A 8.03±1.28	<0.8 <0.001
Chlordiazepoxide	1.0	10 10	L 80.78±2.49 A 6.16±1.99	L 80.77±2.74 A 3.11±0.78	<0.9 <0.2	10 10	L 124.7 ± 4.6 A 10.68± 2.85	L 131.45±4.08 A 12.43±3.34	<0.05 <0.1
Promethazine	0.507	6 6	L 78.0 ±7.16 A 2.38±0.40	L 77.4 ±7.54 A 1.15±0.28	<0.9 <0.02	6 6	L 119.12±10.44 A 6.27± 1.03	L 124.58±8.94 A 7.22±1.19	<0.2 <0.4

The latency (L) is expressed in milliseconds after the light flash and the amplitude (A) in microvolts. A before-after paired comparison student "t" test was used to determine the probability value of significance.

statistically significant ($P < 0.4$). On the other hand, the amplitude of the postive wave 4 in the secondary complex was greatly enhanced, being almost doubled, and the significance of this factor was confirmed statistically ($P < 0.001$). There was no significant change in the latency of this response.

Figure 4 illustrates the effect of secobarbital sodium on the VER in one case. During the intravenous infusion of dextrose and saline, the VER pattern recorded as a reference was characteristic for a person fully awake. As repetitive sets of light flashes were averaged the previously noted rhythmic afterdischarge gradually disappeared, and was no longer prevalent after the fourth set even though the primary and secondary complexes could still be identified. Shortly after the administratoin of secobarbital sodium, while the subject was still awake, the primary complex was now considerably diminished and the secondary complex enhanced. Within 20 minutes after the injection the subject was in profound sleep, with marked diminution of the primary complex and enhancement of the secondary complex. There was no rhythmic afterdischarge and the EEG showed no alpha-like rhythm. The drug-induced sleep resembled natural sleep.

CHLORDIAZEPOXIDE: Chlordiazepoxide hydrochloride, as could be expected, had a depressant effect much less intense than that of secobarbital; however, most of these subjects did tend to fall asleep. Although the record-

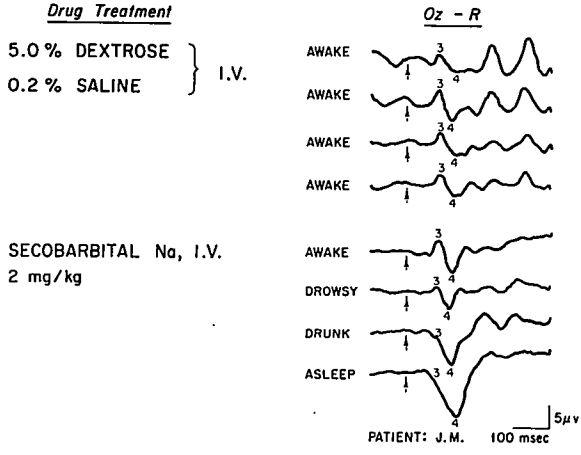

FIG. 4. Effects of secobarbital sodium on the VER in man. Note progressive reduction in wave 3 and enhancement of wave 4 after the administration of secobarbital.

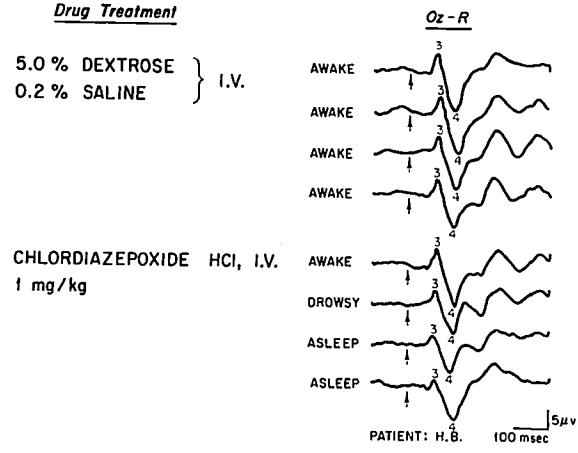

FIG. 5. Effects of chlordiazepoxide hydrochloride on the VER in man. Note that a reduction of wave 3 following the administration of chlordiazepoxide is detectable but that these changes are not as pronounced as shown with secobarbital in figure 4.

ings showed a tendency toward a decrease in amplitude of the primary complex, especially wave 3, the decrease was not statistically significant. There was no effect on the latency of response of wave 3; while the latency of wave 4 tended to increase, the difference was barely significant ($P = 0.05$). The amplitude of wave 4 tended to increase also, but since this factor varied considerably among the patients it could not be considered statistically significant. In general, the effects of chlordiazepoxide may be described as differing from those of secobarbital only in degree.

Figure 5 shows the effects of chlordiazepoxide on the VER in one case. During the dextrose-saline infusion the patient remained awake, and a clear-cut primary-secondary complex was recorded. Five minutes after the administration of chlordiazepoxide hydrochloride the subject was still awake and showed an essentially normal VER. As the subject became drowsy and lapsed into a light sleep the primary complex was clearly reduced. No marked changes in the amplitude of the secondary complex were noted.

SUBSTITUTED PHENOTHIAZINES: As with the other preanesthetic medications, both chlorpromazine and promethazine hydrochloride were given as intravenous infusions over a 5-minute period. After chlorpromazine, the patients characteristically showed marked motor restlessness. Although they would close their eyes and try to relax, bizarre motor movements were frequently observed. The patients were somewhat apprehensive, and after they appeared to be asleep motor restlessness continued. This combination of hyperactivity and anxiety forms a characteristic state of initial turbulence which has been noted before but has not been emphasized. Occasionally a patient complained of pain along the course of the vein in which the injection had been made. No significant changes in blood pressure were observed. VER recordings showed no significant change in the amplitude or latency of the primary complex. The latency of wave 3 was slightly prolonged, but not to a significant degree; the prolonging of latency in wave 4 was statistically significant, however ($P < 0.05$). On the other hand, wave 4 showed no significant change in amplitude.

In contrast to the effects of chlorpromazine, promethazine in equimolar doses produced much less initial turbulence, and the injection was somewhat less irritating. Some motor hyperactivity appeared early in the sleep phase, but this was not marked. There was no significant change in latency of waves 3 and 4. There was a significant reduction in amplitude of wave 3 ($P < 0.02$); the ampli-

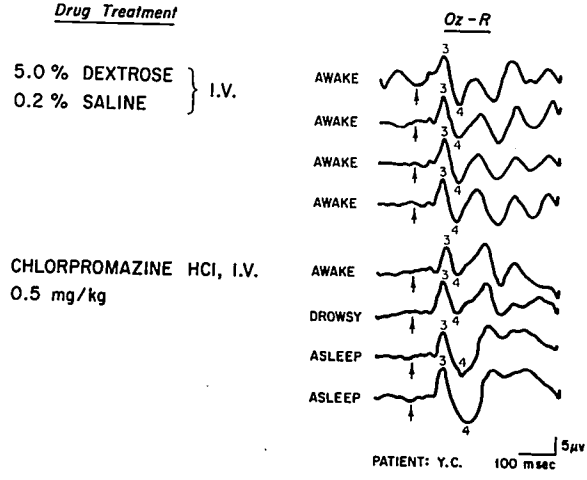

FIG. 6. Effects of chlorpromazine hydrochloride on the VER in man. Note that the primary complex is not depressed after the administration of chlorpromazine although the latency of wave 4 is slightly prolonged.

tude of wave 4 tended to increase, but not significantly.

The effects of chlorpromazine on the VER in one case are shown in figure 6. The initial recording for this patient showed a marked primary complex and a clear-cut secondary complex. It can be seen that chlorpromazine administration did not particularly affect the primary complex, whereas the secondary complex showed early enhancement of wave 5 and decrease in wave 4. As the patient became drowsy and finally fell asleep the primary complex was still evident; the secondary complex, especially wave 4, became enhanced.

Figure 7 shows the effects of promethazine on the VER in one case. Here it can be seen that the primary complex was progressively reduced as the patient fell asleep. In contrast, the secondary complex, especially wave 4, tended to increase.

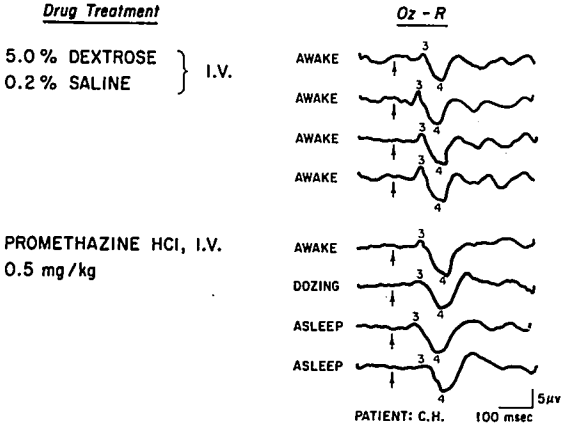

FIG. 7. Effects of promethazine hydrochloride on the VER in man. Note a progressive reduction of wave 3 of the primary complex after the administration of promethazine.

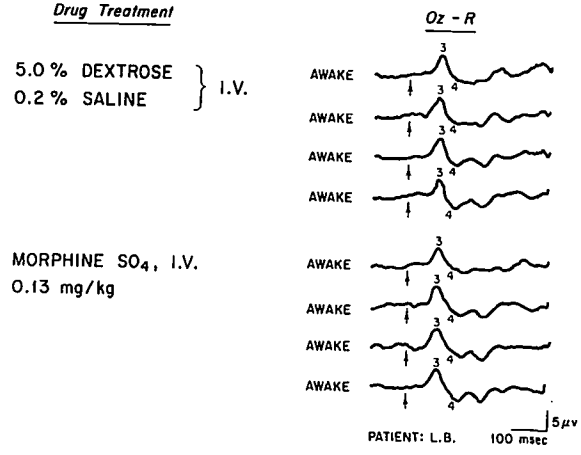

FIG. 8. Effects of morphine sulfate on the VER in man. Note that neither the primary nor the secondary complex are significantly altered following the administration of morphine sulfate.

The difference between chlorpromazine and promethazine in their effects on VER in man appears to be related to the property in chlorpromazine that causes initial turbulence followed by restlessness in sleep, with an associated lack of change in the VER primary complex. The effects of promethazine, on the other hand, appeared quite similar to those of natural sleep, with regard to VER changes.

Effects of Narcotic Analgesia. It may be noteworthy that all of the patients who received morphine sulfate tended to remain awake; none relaxed sufficiently to facilitate normal sleep. There were no significant changes in blood pressure, although the respiration rate showed a transient reduction in some cases. Characteristically, marked pupillary miosis was observed in all instances. In view of these conditions it was not surprising to note little alteration in the VER, as illustrated in figure 8. The configuration of the primary complex underwent insignificant changes after the administration of morphine in this case, and the patient remained awake throughout the entire testing procedure.

Effect of Psychomotor Stimulation. The VER effects of intravenously administered *d*-amphetamine sulfate were observed in 6 cases, in 3 of which the patients received a second dose of 0.05 mg./kg. about 30 minutes after the first dose, for a total dose of 0.1 mg./kg. In none of these cases were there any particular changes in behavior, blood pressure, heart rate, or VER. Paradoxically, two of the subjects showed an increase in alpha rhythm after the drug was administered; this was not noted in the other cases. No side effects were noted except occasional dryness of the mouth.

Effects of Muscarinic Cholinergic Blocking Drugs. Although these agents exert similar peripheral muscarinic blocking actions, their effects on the central nervous system differ considerably, so that the VER of drugs with chiefly peripheral action could be expected to differ from that of central depressant compounds. Table 2 summarizes the effects of the agents selected for our study, with respect to waves 3 and 4; differences in latency were occasionally found which, although minor, were statistically significant. For example, with a dose of 0.0046 mg./kg. of atropine an increase in the latency of wave 3 was observed ($P < 0.001$); surprisingly, the larger dose, 0.0092 mg./kg., did not cause any significant change in the latency of this response. With *l*-hyoscyamine, neither dosage level affected the wave 3 latency significantly. Latency in wave 4 was not affected by either drug. Thus, the general conclusion is that atropine and *l*-hyoscyamine do not markedly affect either the primary or secondary complex

TABLE 2. Effects of Various Muscarinic Cholinergic Blockers on Certain Components of the VER

Drug	Dose (mg./kg.)	Wave 3				Wave 4			
		N	Before ± S.E.	After ± S.E.	P Value	N	Before ± S.E.	After ± S.E.	P Value
Atropine	0.0046	13	L 75.4 ±5.01	L 80.2 ±4.91	<0.001	12	L 122.5 ±4.44	L 124.86 ±4.61	<0.3
		13	A 2.6 ±0.68	A 2.8 ±0.56	<0.5	13	A 7.85 ±1.66	A 7.46 ±1.52	<0.6
Atropine	0.0092	14	L 80.2 ±4.11	L 81.4 ±3.62	<0.6	14	L 123.01 ±6.01	L 127.29 ±6.28	<0.1
		14	A 10.3 ±2.88	A 9.2 ±2.13	<0.2	14	A 11.29 ±3.05	A 11.1 ±1.73	<0.9
l-Hyoscyamine	0.0049	10	L 77.4 ±4.26	L 78.2 ±4.11	<0.7	12	L 122.2 ±8.97	L 123.0 ±8.61	<0.7
		11	A 3.6 ±1.78	A 3.5 ±1.1	<0.9	12	A 10.2 ±2.13	A 8.5 ±1.29	<0.1
l-Hyoscyamine	0.0098	7	L 77.9 ±4.2	L 80.0 ±3.52	<0.3	8	L 125.63 ±7.07	L 125.0 ±6.57	<0.8
		8	A 4.5 ±1.81	A 3.7 ±1.93	<0.4	8	A 12.5 ±2.2	A 10.9 ±2.27	<0.01
Scopolamine	0.0060	12	L 78.5 ±3.36	L 87.15 ±4.46	<0.01	12	L 122.9 ±6.39	L 134.08 ±7.02	<0.02
		14	A 8.88 ±1.92	A 5.3 ±1.51	<0.001	12	A 13.86 ±2.18	A 16.25 ±2.3	<0.1
Scopolamine	0.0070	7	L 77.86 ±5.36	L 77.86 ±3.38	<0.9	7	L 131.07 ±7.5	L 136.78 ±8.12	<0.2
		7	A 10.6 ±2.06	A 6.7 ±2.73	<0.1	7	A 16.39 ±4.78	A 19.7 ±4.36	<0.2
Methscopolamine	0.0055	10	L 78.39 ±3.98	L 77.2 ±2.86	<0.6	9	L 119.7 ±4.14	L 120.36 ±4.78	<0.7
		11	A 2.85 ±0.50	A 3.2 ±0.53	<0.2	9	A 6.17 ±1.07	A 5.96 ±1.52	<0.6

The latency (L) is expressed in milliseconds after the light flash and the amplitude (A) in microvolts. A before-after comparison student "*t*" test was used to determine the probability value of significance.

of the VER, a conclusion that may be related to the fact that these agents do not produce central nervous sedation—in fact, atropine at least has been reported to produce some central stimulation.

In contrast to the relative lack of effects with atropine and *l*-hyoscyamine, scopolamine exerted significant depressant actions on the primary complex of the VER, increasing the latency and decreasing the amplitude of wave 3. Both latency and amplitude of the secondary complex appeared to be enhanced. At a higher dosage level the VER alterations were similar but in greater degree. In general, the effect of scopolamine on the VER was similar to that produced by natural sleep, in accordance with the basic clinical knowledge that scopolamine characteristically promotes sleep.

An interesting comparison was made between scopolamine hydrobromide and its quaternary analogue methscopolamine bromide. Although the analogue exerts all the peripheral effects of scopolamine and is in fact more potent, it lacks the sedating property of the latter because the quaternary compound is known to penetrate the blood-brain barrier with difficulty. When the two agents were compared at equimolar dosage levels, methscopolamine produced no significant change in the amplitude or latency of waves 3 or 4, in contrast to the actions of scopolamine (table 2; fig. 9).

Discussion

Modern electronic averaging devices have greatly simplified the recording of visually evoked responses in man, so that in an electroencephalographic procedure the evoked potentials may readily be distinguished from background activity. Many investigators have suggested their own terminology for the wave forms associated with respective occipital scalp leads. We have favored the terms used by Cigánek,[4] who systematically studied in man the effects of natural and induced sleep on the VER.

Cigánek concluded that natural sleep, thiopental anesthesia and chlorpromazine sedation did not produce any significant changes in the primary evoked response, which he reported (waves 1 through 3) to be unaltered except for a prolonged latency. He found the secondary responses to be enhanced and noted that the rhythmic afterdischarge tended to disappear. The results of our study, however, indicate that during natural sleep the primary complex is not only slowed but depressed, while the secondary complex increases markedly in amplitude in accordance with the depth of sleep. Ebe and co-workers[7, 8, 9] reported somewhat similar findings, and said that the intensity of the light-flash must be taken into account for proper interpretation of the VER. They found that although the

amplitude of the response was considerably greater during sleep than while awake, the threshold to the flash-stimulus was more than a thousand-fold higher during sleep. In our experiments, in which the intensities of light were relatively low and were kept constant throughout, a marked reduction in the primary complex and enhancement of the secondary complex (especially wave 4) was frequently observed in both natural and drug-induced sleep. It is difficult to decide whether the depression of the primary complex (waves 1 through 3) represents reticular inhibition of sensory input while enhancement represents a lack of such inhibition, or whether such changes in the VER result from decreased or increased synchrony of unit discharge. Perhaps because of the long duration of averaging, an enhancement of the primary complex, particularly wave 3, during light sleep was rarely seen. On the other hand, the amplitude of wave 4 in the secondary complex was clearly and significantly enhanced especially during natural and drug-induced sleep.

The observations made with muscarinic cholinergic blocking agents are especially interesting. Scopolamine hydrobromide clearly is unique with respect to all the other agents studied. The actions of this drug in prolonging the latency of both primary and secondary complexes, decreasing the amplitude of the primary while enhancing the secondary complex is quite in accordance with its well-known sleep-producing characteristics. In contrast, methscopolamine, known to be more potent in muscarinic-blocking,[10] showed no such effects on VER, presumably because as a quaternary analogue it cannot easily penetrate the blood-brain barrier. The actions of scopolamine are probably due to a direct central effect rather than peripheral, a conclusion strongly supported by the observation that

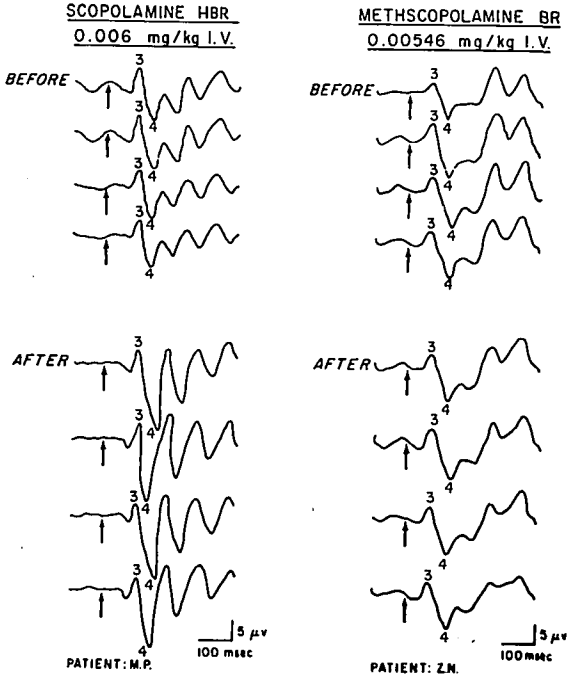

FIG. 9. Differential actions of equimolar doses of scopolamine hydrobromide and methscopolamine bromide on the VER in man. Note that scopolamine reduces wave 3 of the primary complex, enhances the secondary complex and the rhythmic afterdischarge while methscopolamine has no significant effect.

atropine and *l*-hyoscyamine did not significantly alter the amplitude of the primary and secondary complex. Changes in pupillary size, therefore, cannot explain the actions of scopolamine. In some instances atropine and *l*-hyoscyamine appeared to prolong latency, but this was not a consistent finding when the dosage was increased.

Our early impressions[1,2] that atropine had a stimulating effect resulting in a significant increase in the amplitude of wave 3 were not borne out by more detailed studies and statistical analysis. Although such an effect was noticeable in some cases, the overall increase in amplitude was too slight to be statistically significant. Therefore, we are unable to add to the evidence for or against the hypothesis that atropine is a cortical stimulant in man.

Our limited studies with the psychomotor stimulant, *d*-amphetamine, suggest that with the relatively low doses used there is no significant effect on the VER. This seems to correlate with the observation that our patients showed no significant psychomotor stimulation from these doses of d-amphetamine.

From the data presented it may be concluded that VER in man can be a valuable tool for the objective measurement of the efficacy of preanesthetic drugs to suppress visual sensory input and promote sleep. As other afferent systems, particularly pain, will be studied in the future applying evoked response techniques, it may be possible to select preanesthetic agents as to their effectiveness to block various afferent systems thereby producing optimal conditions for the induction of general anesthesia in man.

Summary

Visual stimulation by a flash of light directed into the eyes is especially suitable for studying sensory input in man under varying conditions. With the aid of electronic averaging devices the visually evoked response can readily be distinguished in electroencephalographic tracings. In this study the technique was applied to objectively measure cerebral effects of various drugs used in preanesthetic medication. Responses were obtained before and after the administration of the agents in 124 patients scheduled for operation.

Sedative drugs tested included secobarbital, chlorpromazine, promethazine, and chlordiazepoxide. Except for chlorpromazine, these drugs tended to depress the primary complex and enhance the secondary, especially in those instances where "natural" sleep was induced. With the substituted phenothiazines, a state of anxiety and motor hyperactivity followed soon after the drugs were injected, the reaction being more pronounced with chlorpromazine than with promethazine. After this initial stage of turbulence, however, the characteristic depression usually reported for these drugs was observed. The narcotic analgesic, morphine sulfate, and the psychomotor stimulant, d-amphetamine, did not significantly alter the primary and secondary complexes. Of various muscarinic cholinergic blocking agents studied, scopolamine hydrobromide reduced the VER primary complex to a much greater degree than did *l*-hyoscyamine hydrobromide and atropine sulfate. The latter agents had relatively little effect on VER, and this observation applied also to methscopolamine bromide, a quaternary compound which cannot easily penetrate the blood-brain barrier. With regard to atropine, detailed study and statistical analysis failed to yield evidence either for or against the clinical impression that this drug may exert a cortical stimulant effect.

The results of this study indicate that the VER in man may be of value in objectively measuring the effectiveness and ability of drugs used in preanesthetic medication to suppress visual sensory input and promote sleep. As other afferent systems, particularly pain, will be studied in the future with the aid of averaged evoked response techniques, it may be possible to select preanesthetic agents as to their efficacy to block various sensory inputs and thereby produce optimal conditions for the induction of general anesthesia.

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TETANUS In patients with generalized tetanus in whom respiratory function was considered to be impaired, vital and maximum breathing capacities were low during the acute and benign phases of the disease. Ventilatory volumes returned to normal only after a period of two to three months. Pulmonary compliance, maximal inspiratory and expiratory flow rates were abnormal; reduced ventilatory capacity resulted from a combination of chest rigidity and fixation of the diaphragm; follow-up roentgenographic examination of 2 of the 4 patients showed complete restoration of diaphragmatic motion after 34 to 60 days. Arterial oxygen saturation was not reduced to levels which by themselves could be considered a threat to life. Carbon dioxide retention was not observed. Respiratory failure is rarely the primary cause of death in tetanus. (*Kloetzel, K.: Studies on the Cause of Death in Tetanus, Dis. Chest 45: 63 (Jan.) 1964.*)

HALOTHANE HEPATOXICITY The number of halothane anesthetics administered probably amounts to several millions, yet the number of alleged cases of post-halothane jaundice is presently less than thirty. It is evident that thorough retrospective analyses are needed to establish a truly hard core of cases in which the association of halothane anesthesia and jaundice occurred for reasons other than mere chance or in circumstances which could prove an adequate alternative explanation. Pertinent to the issue is the pathologist's inability to distinguish between lesions of viral hepatitis and those allegedly resulting from halothane. Also, liver damage produced by chemically related agents such as chloroform and carbon tetrachloride varies distinctly from that reported following halothane anesthesia. Considering this and other evidence, there is a distinct impression of uncertainty about the etiology, pathogenesis, and, indeed, the actual existence of halothane hepatotoxicity. Nevertheless, caution is not out of place at this juncture. (*Editorial: Halothane and Jaundice, Canad. Med. Ass. J. 89: 1098 (Nov. 23) 1963.*)