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The Electroencephalogram in Man Anesthetized with Forane

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Electroencephalograms (EEG) of seven healthy male volunteers anesthetized with Forane were studied. Body temperature and Pa_{CO_2} were maintained at normal levels except that hypocapnia was transiently induced once or twice during each study. Increasing doses of Forane produced increasing periods of burst suppression, with complete electrical silence appearing at approximately 2½ per cent end-tidal Forane. At light levels of anesthesia, the frequency of electrical activity was 14 to 17 Hz at a maximum voltage of 120–180 microvolts. At subanesthetic concentrations (below 1.2 per cent) frequency increased and voltage decreased slightly. Hypocapnia did not alter these EEG findings. Audiostimulation could sometimes provoke an EEG response during an electrical silence. In no case was a convulsive EEG pattern (high-frequency, high-voltage spiging activity) seen. Forane-induced EEG changes can be distinguished from those seen with other anesthetics by the maintenance of high-frequency activity at any level where EEG activity is present. Depth of anesthesia can be monitored with the EEG. (Key words: Electroencephalogram; Forane.)

ELECTROENCEPHALOGRAPHIC (EEG) ACTIVITY was studied in human volunteers anesthetized with Forane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether)§ to determine: 1) whether Forane produces convulsive EEG patterns like those observed during anesthesia with enflurane (Ethrane§),[1] an isomer of Forane; and 2) the value of the EEG as an index of anesthetic depth. Our studies in dogs anesthetized with Forane at various anesthetic levels and various Pa_{CO_2}'s did not show convulsive EEG activity (unpublished data). However, these findings had not been confirmed in man.

Methods

Seven healthy male volunteers 23 ± 1 years old were anesthetized with Forane for cardiovascular studies, the results of which have been reported.[2] A description of the preparation of the volunteer prior to and during the study period may be obtained from the previous report. The following points are pertinent to this study: the volunteers were not medicated and were anesthetized with Forane in oxygen. The trachea was intubated and respiration controlled to maintain Pa_{CO_2} between 35 and 40 torr except where indicated. Esophageal temperature was held between 36 and 37 C. Arterial specimens were obtained from an indwelling catheter. End-tidal (alveolar) Forane concentrations and PA_{CO_2} were measured with an infrared analyzer. The EEG was recorded from bitemporal needle electrodes with a Grass recorder. As soon as possible following endotracheal intubation, the alveolar Forane concentrations was brought to 1.2 per cent, held there for 15 minutes to allow equilibration of the brain with the alveolar Forane partial pressure, and the EEG recorded. This procedure was repeated at alveolar concentrations of 1.9 and 2.5 per cent. The Forane concentration then was lowered to 1.3 per cent and the EEG recorded when the alveolar value had been stable for 30 minutes. In six subjects, ventilation was then increased to decrease Pa_{CO_2} from 38 ± 1 (SE) torr to 19 ± 1 torr. Fifteen minutes after the attain-

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ment of the lower Pa_{CO_2} the EEG was again recorded. Following this, ventilation was restored to normal. In three subjects, alveolar Forane was increased to 2.4–2.5 per cent and the EEG again studied at eucapnia and hypocapnia. Five hours after induction of anesthesia, we again measured the EEG at 1.2, 1.9, and 2.5 per cent alveolar Forane. Following this, alveolar Forane concentration was lowered in steps and the EEG measured at each step. Each step was held for a minimum of 10 minutes. The stepwise lowering was continued until the volunteer moved or coughed. A part of every EEG measurement was audiostimulation, produced by hand-claps at the volunteer's ear. This followed a recording of the EEG obtained without stimulation.

EEG tracings were examined for average frequency (average number of all peak-by-peak fluctuations/sec) and maximum peak-to-peak voltage. When burst suppression occurred, average frequency was measured when electrical activity was present only. The average duration of the bursts of electrical activity was measured. Means and standard errors were calculated and compared by a paired t test. We accepted $P < 0.5$ as significant. Regression analyses were done by the method of least squares.

Results

The EEG progressed from continuous activity at 1.2 per cent to burst suppression at 1.9 per cent and complete electrical silence at 2.5 per cent (fig. 1; table 1). Although some statistically significant differences between the early and late patterns appeared, for all practical purposes they were identical. At the lighter level of anesthesia the average frequency usually lay between 15 and 18 Hz with a maximum voltage swing between 110 and 150 μv. In only one case did we find burst suppression at this level. At 1.9 per cent, burst suppression appeared in half the volunteers. During periods of electrical activity frequency was slightly but significantly less than frequency at the lighter level, while voltage increased insignificantly.

At 1.3 per cent Forane, hypocapnia increased frequency insignificantly and left voltage unchanged (table 2). In no case was high-voltage spiking activity seen. In the few

TABLE 1. Effects of Anesthetic Duration and Dose on the EEG

Time (Min)	N†	Alveolar Forane (Per Cent)	P_{ACO_2} (torr)	Hz‡/N	Number of Subjects Evincing Electrical Silence/N	Maximum Peak-to-peak Voltage (μv)/N	Average Duration of Burst (sec)/N	Average Duration of Silence (sec)/N	Per Cent of EEG That Was Silent/N
38 ± 3	7	1.23 ± 0.02	35.4 ± 1.0	16.8 ± 0.3/7	1/7	138.0 ± 12.0	70/1	47/1	5.3 ± 5.3/7
59 ± 4	7	1.87 ± 0.03	37.1 ± 1.0	15.1 ± 0.5/5	4/7	170.0 ± 12.3	81/3	37/3	31.3 ± 14.4
77 ± 3	7	2.40 ± 0.03	37.0 ± 1.0	Total silence	7/7	Total silence	Total silence	Total silence	100/7
285 ± 8	7	1.23 ± 0.02	37.7 ± 0.8	15.8 ± 0.3/7	0/7	127.1 ± 10.3/7	—	Total silence	0.7
305 ± 8	7	1.80 ± 0.03	38.4 ± 1.7	13.9 ± 0.6/5	3/7	166.0 ± 14.4	94/2	57/2	23.6 ± 14.0/7
324 ± 9	7	2.48 ± 0.04	37.8 ± 1.7	Total silence	7/7	Total silence	Total silence	Total silence	100/7

* Minutes from the start of induction.
† N is the number of subjects used in a particular measurement. Although seven subjects were examined, not all evinced any particular characteristic. For example, at 38 minutes only one subject had burst suppression, and therefore there was only one subject in the measurements of average durations of burst and silence.
‡ Cycles/sec.

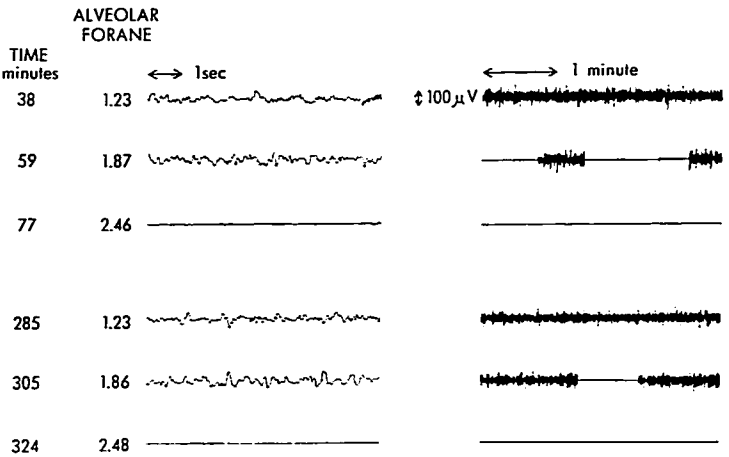

FIG. 1. Bitemporal EEG patterns early (first hour of anesthesia) and late (fifth hour) at various alveolar Forane concentrations. Normocapnia was maintained throughout. The tracings on the left were taken at a fast paper speed to illustrate the character of EEG frequency at the various anesthetic levels. The tracings on the right were taken at a slow paper speed to illustrate the increasing periods of electrical silence that appear as Forane concentrations are increased.

TABLE 2. Effects of P_{ACO_2} Changes on the EEG

N	Alveolar Forane (Per Cent)	P_{ACO_2} (torr)	Hz	Maximum Voltage (μv)	Silence (Per Cent)
6	1.31 ± 0.01	38.9 ± 1.3	14.7 ± 0.98	136 ± 19	—
6	1.21 ± 0.01	19.6 ± 1.5	16.1 ± 0.54	139 ± 18	—
3	2.51 ± 0.05	36.3 ± 2.3	—	—	95.5
3	2.42 ± 0.10	23.5 ± 1.9	—	—	100

TABLE 3. Effects of Audiostimulation on the EEG

N	Alveolar Forane (Per Cent)	P_{ACO_2} (torr)	Hz/N	Number of Subjects Evincing Electrical Silence/N	Maximum Peak-to-peak Voltage (μv)/N	Average Duration of Burst (sec/N)	Average Duration of Silence (sec)/N	Per Cent of EEG That Was Silent/N
6	2.46 ± 0.04	38.6 ± 1.6	—	6/6	—	60/1	150/1	97.5 ± 2.5/6
6	1.90 ± 0.03	30.2 ± 1.0	13.4 ± 0.6/6	1/6	136.7 ± 12.3/6	41/1	59/1	11.0 ± 11.0/6
6	1.42 ± 0.02	31.7 ± 1.4	14.8 ± 0.4/6	0/6	140.0 ± 14.5	—	—	0/6
5	1.19 ± 0.005	31.4 ± 1.5	15.3 ± 0.4/5	0/5	124.0 ± 7.5	—	—	0/5
6	1.01 ± 0.02	32.2 ± 1.7	16.6 ± 0.5/6	0/6	95.8 ± 11.4	—	—	0/6
6	0.79 ± 0.03	31.8 ± 1.6	18.6 ± 0.7/6	0/6	58.3 ± 7.9	—	—	0/6

* Arterial sample.

subjects studied at the deeper level of Forane anesthesia, electrical silence predominated and was not reversed by hyperventilation.

Decreasing alveolar Forane below 1.9 per cent resulted in a progressive increase in frequency which was significant on comparison of light *vs.* deeper levels of anesthesia. Similarly, a significant decrease in voltage appeared as the end-tidal concentration was lowered below 1.4 per cent (fig. 2; table 3). At 1.9 per cent Forane or less, CO_2 was measured in alveolar gas rather than arterial blood. Since 4–8-torr arterial-to-alveolar CO_2 differences existed for most subjects, this represented a Pa_{CO_2} of approximately 40 torr.

Hand clapping did not produce a convulsive pattern in the EEG of any volunteer during either eucapnia or hypocapnia or at any level of anesthesia. In the EEG's of two volunteers, clapping during moderate or deep anesthesia occasionally provoked a response which culminated in the reappearance of electrical activity (fig. 3). At no time did we observe twitching or jerking of peripheral muscles.

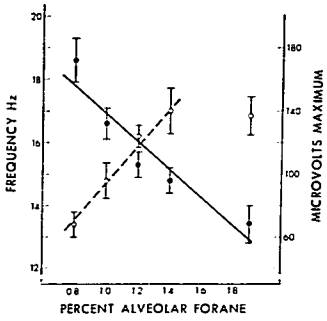

FIG. 2. The changes in frequency (left ordinate, filled circles) and maximum voltage amplitude (right ordinate, open circles) produced by progressive stepwise lowering of Forane from 1.9 per cent. The bars about each point represent standard error (n = 6). The lines through each set of points were obtained from the total points (rather than the averages plotted here) by the method of least squares. The slope for frequency *vs.* Forane was −4.39, with a correlation coefficient of −0.95. For microvolts *vs.* Forane (the 1.9 per cent point excluded) the slope was 11.9 and the correlation coefficient was 0.99.

Discussion

In volunteers, Forane did not produce high-frequency, high-voltage electrical activity or abnormal peripheral muscular movement. This contrasts with the findings in studies of the dog and man anesthetized with enflurane, in which convulsive patterns and jerking, and sometimes convulsive muscular movements,

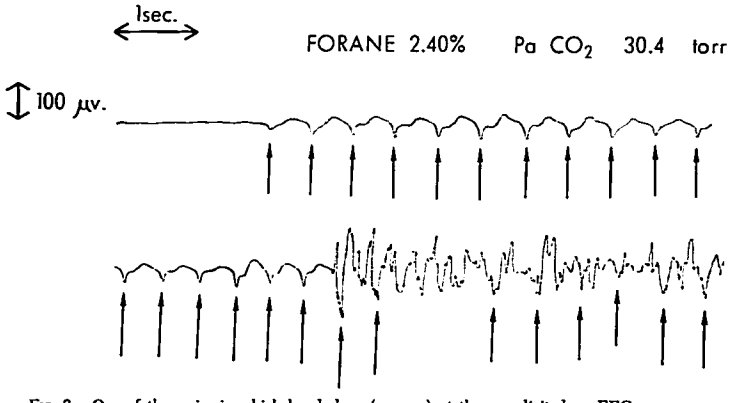

FIG. 3. One of the series in which hand-claps (arrows) at the ear elicited an EEG response. Alveolar Forane was 1.9 per cent with normocapnia.

have been observed.[1] We could not provoke a convulsive pattern with Forane at depths of anesthesia sufficient to abolish all electrical activity or with hypocapnia at any level of anesthesia (fig. 1, 3).

The EEG patterns seen during Forane anesthesia both resemble and differ from those seen with the other commonly used anesthetics. As with other agents, durations of electrical silence with Forane relate directly to increases in anesthetic depth (table 1; fig. 1).[2-6] However, during the periods of activity between burst suppression the frequency of the EEG is sustained at higher Hz with Forane than with other agents. As with other agents, voltage increases at moderate anesthetic depth (fig. 2). However, the peak voltage amplitude is less than those seen with ether,[3] halothane,[4] cyclopropane,[5] or fluroxene.[6] It is possible to use the EEG as an index of depth of Forane anesthesia under the circumstances of this study. Probably the best sign of depth is the appearance of burst suppression, which hails the development of moderate or (when suppression is complete) deep anesthesia. It is not known whether these EEG responses to Forane would be modified by nitrous oxide, premedication, anesthetic adjuvants, increase in Pa_{CO_2}, surgical stimulation, or change in patient age or physical status.

The occasional responses to hand-clapping are of interest in that they suggest perception of auditory stimulation at surgical levels of anesthesia.¶ This accords with findings with other anesthetics.[7, 8] As suggested by French *et al.*,[9] transmission of afferent impulses through the lateral sensory pathways may persist at anesthetic doses which impair transmission through the reticular formation. Thus, our work indirectly supports the notion that the site of anesthetic action lies in the reticular formation.

¶ MAC in this age group is about 1.3 per cent (Stevens, W. C., unpublished data).

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