THE ELECTROENCEPHALOGRAM DURING CHLOROFORM ANESTHESIA

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CHLOROFORM has been employed in many thousands of instances for the production of general anesthesia since its introduction for this purpose by Simpson in November 1847. But it has been abandoned or avoided by many physicians because of the acquired stigmata of its producing "cardiac syncope" and sudden death, and of its being toxic to the liver and kidneys. Waters and his associates after re-evaluating this agent,[1] have suggested several future developments that would be desirable to increase the safety of the administration of chloroform. One such development was a method for estimating the depth of anesthesia, for they believed that the physical signs of depth during chloroform inhalation were unreliable. This suggestion has provided the stimulus for the present study.

The recent development of versatile calibrated vaporizers and their clinical application for the administration of chloroform provides a safeguard against overdose, which has long been recognized as necessary and desirable.[1, 2] Physiological variations in the uptake of volatile anesthetics suggest that continuous estimates of the depth of anesthesia obtained by monitoring the electroencephalogram (EEG) should be utilized to provide a safeguard during the clinical use of this agent. We were able to locate only two examples in the literature of the EEG in man during chloroform anesthesia.[3]

The present study was undertaken to characterize the EEG levels of chloroform anesthesia in man and to determine whether there was a useful correlation between these levels and the concentration of chloroform in arterial blood and the clinical estimates of the depth of anesthesia.

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MATERIALS AND METHODS

Twelve female patients 19 to 32 years of age and free of cardio-pulmonary and hepatic disease, as determined by clinical examination, were studied. These patients scheduled to undergo minor operative procedures received atropine, 0.6 mg., intramuscularly one hour before operation. Before induction of anesthesia, standard electrocardiographic (ECG) limb leads and EEG needle electrodes were placed in position. Lead 1 or 2 of the ECG, and the fronto-occipital lead of the EEG from the dominant hemisphere were continuously monitored during this study on an Eden Anesthograph.

Under local anesthesia an 18 gauge needle was placed in a brachial or femoral artery for the withdrawal of arterial blood samples. Anesthesia was then induced and maintained with chloroform and oxygen alone, using a semiclosed carbon dioxide absorption system and a total flow of 5 liters per minute. Chloroform was vaporized from a "copper kettle" and the concentration was determined by calculation from the vapor pressure and total flow. The inspired concentration of chloroform was increased gradually from zero to 2 or 2.5 per cent and remained at this level throughout the study. In one instance, to obtain level VI, the inspired concentration was allowed to reach 4 per cent for a brief period. Supplementary agents such as thiopental and muscle relaxants were not used and the trachea was not intubated in any patient during the course of this study. Respiratory exchange was augmented by manual compression of the rebreathing bag as the depth of anesthesia was deepened.

Arterial blood samples were obtained during the induction and maintenance phases of anesthesia and before the start of surgery. These samples were refrigerated until analysis for chloroform could be performed, usually

less than four hours. This analysis was performed by the toluene extraction method, as modified by Conner and Fleitz.[4] Arterial blood samples were not taken during surgery nor during the recovery period for purposes of this study.

The chloroform content of the inspired gas mixture was not measured in this study. However, the concentration delivered into the semiclosed circle system was not allowed to exceed 2.5 per cent except in one instance (4 per cent). Since a 5-liter per minute total flow assured considerable lung washout, and since chloroform uptake is great before blood-gas equilibrium is achieved, it is doubtful that the inspired concentration of chloroform greatly exceeded that delivered into the system at any time.

Results

EEG Levels and Arterial Blood Chloroform Concentrations. The progression of changes in the EEG during chloroform anesthesia in man can be subdivided into six distinct patterns designated as levels I through VI, as the depth of anesthesia increases. These patterns are shown in figure 1 and can be briefly described as follows.

Level I: A control tracing of low voltage, fast activity is replaced by bursts of 8 to 10 per second waves, with voltage about twice that of the control. These bursts last as long as one second but the majority last only about 0.3 second. Grouping of these waves into bursts is characteristic of level I, chloroform anesthesia. The mean chloroform concentration in arterial blood during level I was 4.8 mg. per 100 ml. of blood, with a standard deviation of 2.43.

Level II: Waves of a frequency of 7 to 10 per second, having an amplitude of 50–75 microvolts and a superimposed low voltage, fast activity, become constant. Onset of level II is quite abrupt and well marked in the EEG record. The mean chloroform concentration during level II was 9.6 mg. per cent with a standard deviation of 1.4. The difference of mean chloroform concentration between levels I and II is statistically significant ($P < 0.01$).

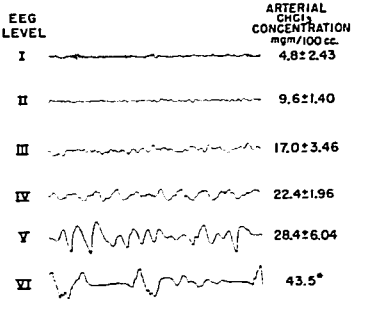

Fig. 1. Patterns characteristic of successive electroencephalographic levels of chloroform anesthesia in man, with associated arterial chloroform concentrations.

Level III: This level is characterized by the abrupt appearance of waves with a frequency of 4 to 7 cycles per second. The amplitude is much greater than in level II, usually over 100 microvolts. Some tracings show low voltage, fast activity superimposed, while others show occasional waves of slower frequency. The mean chloroform concentration during level III was 17 mg. per cent with a standard deviation of 3.46. The mean concentration for EEG level III is significantly greater ($P < 0.01$) than the concentration required to produce level II.

Level IV: This level is characterized by waves of 2 to 3 cycles per second and an amplitude of greater than 100 microvolts. Activity of 4 to 7 cycles per second may be superimposed or intermixed for short periods of time. The mean chloroform concentration for level IV was 22.4 mg. per cent and the standard deviation was 1.96. Again, the mean concentration for level IV is significantly greater than the mean concentration for level III ($P < 0.01$).

Level V: Pronounced slow wave activity with greatly increased amplitude characterizes this level. The faster frequencies gradually drop out as level V progresses. Only four patients were carried to level V and chloroform concentration was 28.4 mg. per cent with a standard deviation of 6.04. This mean

concentration is not significantly greater than the mean concentration for level IV.

LEVEL VI: Very large, slow waves appear at frequencies of 0.5 to 1.5 per second, separated by periods of near electrical silence. These periods of apparent silence are as long as one second. Only one patient was carried to this level and the blood chloroform concentration at this time was 43.5 mg. per cent. Marked hypotension was present at this time, and may have influenced the EEG pattern. This depth is excessive and should not be necessary in clinical practice.

The over-all pattern observed in the EEG during chloroform anesthesia was one of increasing amplitude and decreasing frequency as anesthesia deepened. Burst suppression, characteristic of anesthesia with ether and cyclopropane, was not observed during chloroform anesthesia until alarming depth was achieved.

When the observed EEG levels are plotted against the mean chloroform concentration in arterial blood (fig. 2) an almost linear relationship is observed. Level VI is excluded,

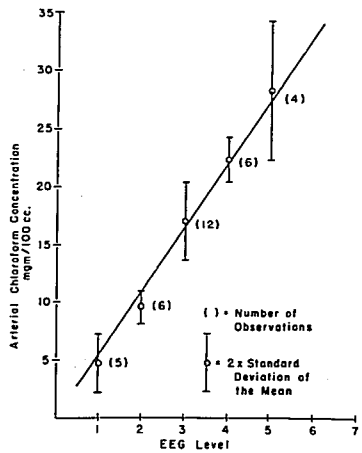

FIG. 2. Correlation of electroencephalographic levels of anesthesia in the human with concentrations of chloroform in arterial blood.

TABLE 1

PULSE RATE DURING CHLOROFORM ANESTHESIA COMPARED WITH CONTROL OBERVATIONS

Status	Pulse Rate		t	Significance Level
	Mean	S.D.		
Control (awake)	80	± 5.52	—	—
EEG Level I	85	± 4.35	1.210	Not significant
II	74	±16.0	0.292	Not significant
III	74	± 3.98	1.550	Not significant
IV	78	± 5.45	0.319	Not significant
V	80	±12.3	—	No difference in means
VI	69	—	—	One determination

S. D. = standard deviation.

because we had only one observation at this level.

Electrocardiographic Changes. Lead 1 or 2 of the ECG was continuously recorded in all patients. Cardiac rhythm was little affected during this study. Minor and transient T waves and ST segment changes were observed in 5 of the 12 patients. Occasional premature ventricular contractions were also observed. Only one serious arrhythmia was encountered. Bigeminal rhythm appeared in a patient whose arterial blood chlorform concentration was 25 mg. per cent. This arrhythmia reverted to normal sinus rhythm within 80 seconds when the administration of chloroform was discontinued. The highest blood chloroform concentration attained (43.5 mg. per cent) was associated with a normal electrocardiogram.

Pulse Rate. The pulse rate was determined from the ECG of each patient before induction of anesthesia and again at each EEG level, and these data are presented in table 1. No significant change in the pulse rate was found during chloroform anesthesia under the conditions of this study.

Arterial Blood Pressure. Arterial blood pressure was not monitored continuously during this study, but blood pressure was estimated frequently by the auscultatory method. Arterial blood pressure was well maintained during EEG levels I, II and III. Beginning level IV, there was usually a gradual decline in arterial pressure and by the time a level V was reached, moderate hypotension was usually observed. Level VI was associated with marked hypotension.

Discussion

The only previously published EEG tracings during chloroform anesthesia in man are by Berger in 1931.[3] One of these records is reproduced as figure 3. The time scale is different but otherwise the tracing is similar to those we have observed. Figure 3 appears to represent EEG level II.

The EEG during chloroform anesthesia in the dog has been carefully studied by Pearcy and associates,[5] and the findings in the dog are similar to those in man. Their tracings were also characterized by increasing voltage and decreasing frequency as anesthesia progressed, and there was notable lack of burst suppression. The only major differences between the findings of Pearcy and that of the present study are in the first level of anesthesia, where we observed a spindling pattern in man, which was not observed in the dog.

This pattern during level I deserves additional comment. The appearance of these groups of 8 to 10 per second waves, which are in the alpha frequency range, is the first characteristic change observed during the induction of anesthesia with chloroform and oxygen. These wave groupings were observed even in those patients who did not manifest clear-cut alpha activity in the control tracings.

The presence of this type of activity in EEG level I has not been described in reports of EEG patterns with other anesthetic agents. Brechner and Dornette[6] describe "spindling" in the EEG during anesthesia with trifluoroethylvinyl ether, but at a lower frequency and at a deeper level of anesthesia (level II). The recognition of this "spindling" pattern in level I during the present study may be related to the restriction of preanesthetic medication to atropine.

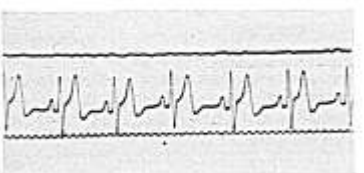

Fig. 3. Upper record shows EEG during light chloroform narcosis from Berger.[3] This approximates level II. (Reproduced with the permission of the publishers, Springer-Verlag, Berlin.)

With the exception of level I, the remainder of the EEG during chloroform anesthesia closely resembles patterns seen with other halogenated hydrocarbon anesthetic agents such as halothane,[7] trifluoroethylvinyl ether[6] and methoxyfluorane.[8] All of these halogenated agents appear to share the property of producing an EEG similarly characterized by decreasing frequency and increasing voltage as anesthesia deepens. Suppression occurs only late, if at all, during anesthesia with the halogenated agents. For example, Pearcy and his associates noted no evidence of burst suppression during chloroform anesthesia in the dog. In the present study, patterns resembling burst suppression appeared only during the deepest level which we were able to attain, and there was marked hypotension at the time. During anesthesia with halothane, Gain and Paletz[7] observed burst suppression only during levels V and VI.

The EEG during anesthesia with chloroform and other halogenated hydrocarbons thus appears to present differences from the patterns observed during anesthesia with ether[9] and cyclopropane.[10] With the latter agents, the greatest amplitude of the EEG appears in levels II and III, and level II is usually characterized by markedly symmetrical and synchronous electrical activity. Beyond level III with ether and cyclopropane, suppression of cortical activity is noted in a progressive fashion, eventually reaching a state of near electrical silence. With chloroform and other halogenated agents, the greatest voltage of EEG usually appears in levels IV and V, with evidence of cortical suppression appearing later. In addition to these differences, the symmetrical and synchronous discharges seen in level II of cyclopropane and ether anesthesia are not observed with chloroform.

There have been few reports in the recent literature on the concentration of chloroform in the blood during anesthesia. The principle studies are those of Pearcy[5] and associates in the dog, and Waters[1] and his group in man. Pearcy's report does not give complete blood data for all levels of anesthesia, but from the data presented we have calcu-

lated a mean value of 25.3 mg. per cent of chloroform in arterial blood to produce level IV anesthesia in the dog. This compares favorably with our mean value of 22.4 mg. per cent for production of level IV anesthesia in man, and both values are in line with older work.[11]

Waters and his group have studied the blood chloroform concentration during anesthesia in man, and attempted to show a correlation with the depth of anesthesia as judged clinically.[1] The values of blood chloroform which they observed are considerably lower in most cases than those which we have encountered. For example, during stage 3, plane 1 anesthesia, they found a mean value of 7.1 mg. of chloroform per 100 ml. of blood while we found a comparable value of 9.6 mg. In the deepest level which they describe, that is, stage 3, plane 4, the Waters group observed a concentration of 13.5 mg. per cent, where in our study a mean value for a similar depth of anesthesia would be approximately 28 mg. per cent.

There are a numer of reasons which may explain the discrepancy between Waters' values of chloroform concentration during anesthesia and ours. The Wisconsin group studied the venous concentration of chloroform rather than the arterial and there is no statement as to what preanesthetic medication the patients received. The use of narcotics as preanesthetic medication would be expected to reduce the concentration of chloroform required to produce a given depth of anesthesia. In addition, analysis for chloroform was performed by the Wisconsin group using a method (pyridine method) which, in our hands, has failed to yield consistent results. However, it must be pointed out that our study was made during the induction and deepening phases of anesthesia at a time when the tissues may still have been taking up chloroform, and it is possible that the arterial concentration at this time might be somewhat higher than concentrations reached after a period of equilibration had been achieved.

Considerable variation in chloroform concentration required to produce a given EEG level in different animals was found by Pearcy *et al.*[5] Variation appears less marked in man. We find an almost linear relationship between the concentration of chloroform in arterial blood and the level of anesthesia as judged by the EEG. While some individuals will show a considerable variation from the mean, we believe that in a majority of patients, a good prediction of the arterial blood concentration of chloroform can be made from the EEG. A linear relationship between depth of anesthesia and concentration of anesthetic agent in the arterial blood has been reported for ether[9] and for cyclopropane.[10]

Correlation between the EEG level of anesthesia and the depth of anesthesia as judged clinically is not always so striking. The EEG of level I always appeared during analgesia but before loss of consciousness. Level II consistently appeared on entering stage 3, plane 1 of clinical anesthesia. As anesthesia deepened, discrepancies between the EEG and the clinical signs of depth were observed more frequently.

The Wisconsin group has stated that the depth of chloroform anesthesia is difficult to assess by the usual clinical signs and symptoms.[1] Our clinical experiences are similar and we believe that the EEG is a more accurate guide to the depth of chloroform anesthesia.

Summary

The EEG has been studied during anesthesia with chloroform and oxygen as the sole agents in patients who received only atropine for preanesthetic medication. The EEG during chloroform anesthesia is characterized by increasing amplitude and decreasing frequency with persistence of activity into deep planes of anesthesia. The patterns resemble those observed during anesthesia with halothane and other halogenated hydrocarbons and differ from those observed during ether and cyclopropane anesthesia. These findings appear to challenge the concept that all anesthetic agents produce fundamentally similar effects on the EEG.

The arterial blood content of chloroform was also studied and a linear relationship found between the EEG level of anesthesia as described in this study and the concentration of chloroform in arterial blood.

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PROCAINAMIDE The effect of procainamide on the heart is similar to that of quinidine: the excitability of the atria and ventricles is reduced; conduction is slowed in the bundle of His and in the myocardium; the threshold to electrically induced fibrillation is increased. Procainamide does not depress myocardial contractility, and has little effect on the central nervous system. Three cases are reported in which there was ventricular fibrillation, refractory to therapy. After the administration of procainamide, defibrillation was successfully accomplished. (*Meyer, J. A., Blumenstock, D. A., and Berry, F. B.: Procainamide Hydrochloride in Ventricular Defibrillation, A. M. A. Arch. Surg. 82: 488 (Mar.) 1961.*)

ANGIOTENSIN A lucid review shows that angiotensinogen is formed in the liver and is converted by the enzyme renin, from the kidney, to angiotensin I, a decapeptide. A converting enzyme in plasma causes the loss of a dipeptide group which leaves the octapeptide angiotensin II, a more active substance which causes contraction of smooth muscle. Angiotensin II, which has been synthesized, is inactivated by the enzyme angiotensinase which is widely distributed in plasma and tissues and is the only substance known to destroy angiotensin in vivo. The relation of angiotensin to essential arterial hypertension is suggestive but not definite. (*Benedict, K. T., Jr.: Angiotensin: Its Biochemistry and Relation to Essential Hypertension, Tufts Folia Med. 7: 23 (Jan.–Mar.) 1961.*)