Anesthesiology
V 35, No 5, Nov 1971

The Electroencephalographic Pattern during Anesthesia with Ethrane:

Effects of Depth of Anesthesia, Pa_{CO_2}, and Nitrous Oxide

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The EEG patterns of increasing depths of Ethrane–O_2 anesthesia and the alterations in the patterns produced by changing Pa_{CO_2} and by addition of 60 per cent nitrous oxide have been evaluated in 30 individuals. Increasing depth of anesthesia was characterized by the appearance of high-voltage spikes, with the subsequent development of spike waves and burst suppression. Maximum depth was marked by a predominance of spike waves and burst suppression. The anesthetic depth and Pa_{CO_2} at which changes occurred have been defined. With elevation of Pa_{CO_2}, indices of cerebral irritability appeared to be reduced, while reduction of Pa_{CO_2} increased their occurrence. The greatest CO_2 effect was seen at inspired Ethrane concentrations of 2.5 per cent or more. The addition of nitrous oxide did not alter the predominant EEG patterns. (Key words: Electroencephalogram; Nitrous oxide; Ethrane; Carbon dioxide.)

CLINICAL STUDIES of Ethrane‡ (1,1,2-trifluoro-2-chloroethyl difluoromethyl ether) have indicated that the agent has merit because of ease of administration, a high degree of patient acceptance, stability of cardiac rhythm, and the ability to produce excellent muscle relaxation.[1–5] Preliminary data show that the compound undergoes limited biodegradation.[6] The rare occurrence of abnormal motor movements and occasional electroencephalographic (EEG) evidence of cerebral irritability during Ethrane anesthesia have caused concern.[1,2,4] These findings have been most frequently associated with deep levels of anesthesia and with hypocarbia. This study was undertaken to identify in man under controlled conditions to EEG patterns characteristic of increasing depths of anesthesia with Ethrane and the alteration in the EEG produced by changing Pa_{CO_2}. The influence of nitrous oxide on the EEG was also evaluated. Our results indicated that Ethrane can be administered in clinically useful concentrations with or without hyperventilation with minimal EEG signs of cerebral irritability, and the addition of nitrous oxide did not appear to alter the EEG importantly.

Methods

Informed consent was obtained from all individuals. Patients agreed to the use of Ethrane during elective surgery, and anesthetic and Pa_{CO_2} levels were selected according to standard anesthetic practices. Healthy subjects agreed to the use of Ethrane over a wider range of anesthetic doses and Pa_{CO_2} levels and accepted the possibility of gross seizure activity. Data was gathered from two groups, 21 individuals (11 healthy subjects and 10 patients) not receiving added nitrous oxide (Group I), and nine patients to whom nitrous oxide was administered in addition to Ethrane (Group II).

Premedication for all individuals consisted of atropine, 0.5 mg iv or im, 15 to 90 minutes before anesthesia. Anesthesia was induced with Ethrane–O_2 or Ethrane–nitrous oxide–O_2. Tracheal intubation was accomplished within 10 minutes without succinylcholine in 15 individuals and with succinylcholine, 60–100

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Received from the School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104. Accepted for publication June 22, 1971. Supported in part by USPHS Research Training Grant 5-P10-GM-215-13 and USPHS Research Grant 5-P01-GM-15430-04 from the National Institute of General Medical Sciences, and by Ohio Medical Products, a Division of Air Reduction Company, Inc.

‡ Trade name of enflurane, marketed by the Ohio Medical Products Division of Air Reduction Company.

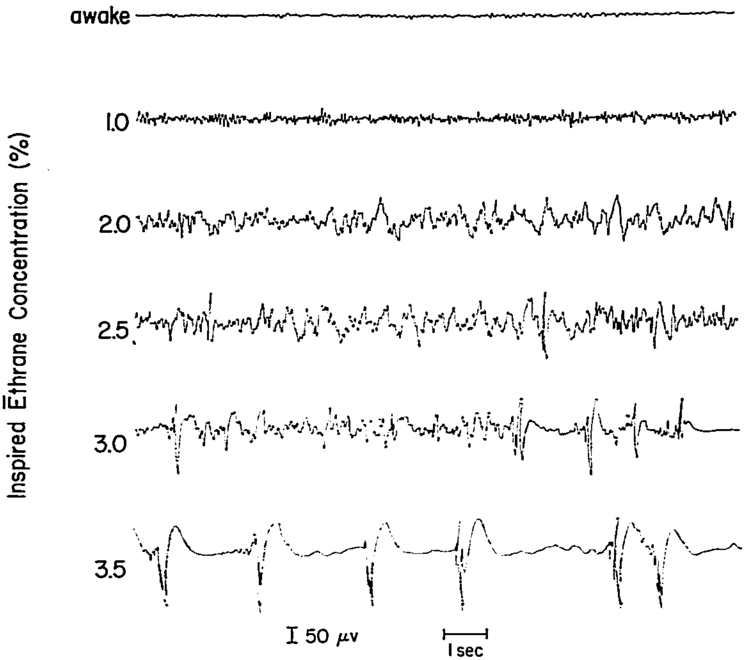

FIG. 1. EEG patterns with increasing depths of Ēthrane anesthesia in one subject at Pa_{CO_2} 35–39 torr.

mg iv, in 15 individuals. Nitrous oxide was then discontinued. In Group II nitrous oxide was later added. Seventy per cent of the individuals received *d*-tubocurarine (mean dose 19 mg) during light anesthesia to prevent movement for experimental purposes and to provide adequate muscle relaxation.

Ēthrane was administered with a Drager vaporizer, Copper Kettle, or Ēthrane vaporizer manufactured by Cyprane Ltd., in either a nonrebreathing or a circle system with a flow greater than 5 L/min. Constant minute ventilation was maintained by a mechanical ventilator at greater-than-normal minute ventilation to produce the lowest Pa_{CO_2} desired. Changes in Pa_{CO_2} were produced by addition of CO_2 to the anesthetic system.

Anesthetic concentrations were measured by a Biomedical Gas Chromatograph, model 400, using volumetrically prepared standards. Inspired gas and mixed expired gas were sampled and a stable anesthetic state was considered to exist when the mixed expired concentration was within 85% of the inspired concentration. Ēthrane concentrations reported are the inspired values when this stable state existed. Arterial blood gases and *p*H were measured by Instrumentation Laboratory electrodes using procedures and correction factors described elsewhere.[7] Steady-state Pa_{CO_2} was achieved by end-tidal monitoring, with a period of at least 15 minutes of stable CO_2 in the healthy subjects and a minimum equilibration period of 30 minutes following a CO_2 change in patients.

The EEG was recorded with a Grass Model

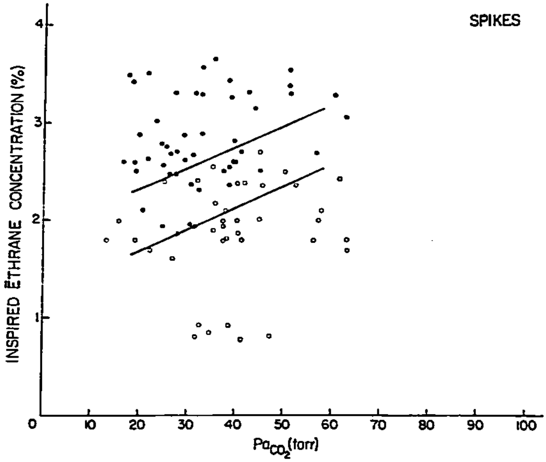

FIG. 2. Spikes of 100 μV or more in 86 observations in 21 individuals. Open circles indicate no spike forms. Closed circles indicate one or more spike forms.

50 polygraph using uni- or bilateral fronto-parietal leads in patients and with a Grass Model G electroencephalograph using six leads in healthy subjects.

Group I

Of the subjects in Group I, eight were maintained at a selected constant Pa_{CO_2} and were exposed to a variety of stable anesthetic states of Ēthrane. Nine were maintained at a selected constant Ēthrane concentration and Pa_{CO_2} was varied. The other four were studied with both: a selected constant Pa_{CO_2} with variation in stable Ēthrane concentrations was followed by a selected stable Ēthrane concentration and varied Pa_{CO_2}.

Group II

Following Ēthrane–O_2 anesthesia, EEG, anesthetic concentration and Pa_{CO_2} were determined. Nitrous oxide, 3 liters, and oxygen, 2 liters, were then added to the same Ēthrane concentration at the same Pa_{CO_2} for 20 minutes before EEG, anesthetic concentration, and Pa_{CO_2} were again measured.

Results

Group I

Increasing the depth of Ēthrane–oxygen was associated with a characteristic change in the EEG. Figure 1 shows the pattern of the change in one subject at Pa_{CO_2} 35–39 torr. As depth increased, spikes (greater than 100 μV) appeared. With further increases in depth, spike waves (a spike followed by a slow wave lasting as long as a second) occurred, and periods of burst suppression developed (electrical silence one second in duration or longer). Maximum depth was associated with a predominance of spike waves and burst suppression.

A one-minute segment of the EEG that indicated maximal irritability at a given Ēthrane concentration and Pa_{CO_2} was analyzed for the presence or absence of spike forms of 100 μV or greater and burst suppression lasting a second or longer. Figure 2 shows the Ēthrane concentration and Pa_{CO_2} at which one or more spike forms during the one-minute period were observed. Three zones can be identified, *i.e.*, a *spike-free area* where all the records showed no spikes, a *transition area*, and a *spike-present area* where spikes were observed under all conditions of Ēthrane and Pa_{CO_2}. The lines, drawn by eye, separate the zones and indicate the increasing occurrence of spikes with increasing anesthetic depth and decreasing Pa_{CO_2}.

The occurrence of burst suppression is shown in figure 3. A similar pattern of three

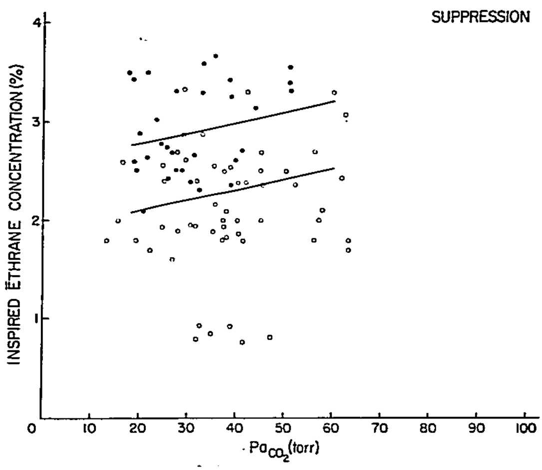

FIG. 3. Burst suppression lasting a second or longer in 86 observations in 21 individuals. Open circles indicate no burst suppression. Closed circles indicate burst suppression.

zones was found. Higher Ēthrane concentrations were needed to produce suppression and Pa_{CO_2} effect was minimal, as indicated by the lesser slopes of the lines in figure 3, compared with those in figure 2.

In an attempt at quantification, the frequencies of spikes and spike waves and the percentages of the one-minute segments occupied by burst suppression were determined in the 29 records made during *normocarbia* (Pa_{CO_2} 35–44 torr, fig. 4). As mean Ēthrane concentration increased, the frequency of spikes increased, then decreased, with a greater frequency of spike waves and longer isoelectric periods.

In the 16 records made during *hypercarbia* (Pa_{CO_2} 45 torr or more) cerebral irritability appeared to be reduced. At mean inspired Ēthrane concentrations of 1.52 and 2.25 per cent, spikes, spike waves and burst suppression did not occur. At a mean inspired Ēthrane concentration of 2.6 per cent, the frequency of spikes was 1/min, with neither spike waves nor burst suppression; at a mean inspired Ēthrane concentration of 3.32 per cent the frequencies of spikes and spike waves were 11.4 and 6.4/min, respectively, and burst suppression occupied 27 per cent of the EEG. Reference to the normocarbic values in figure 4 shows higher frequencies of spikes and spike waves of 7.5 and 3.5/min and a duration of burst suppression of 12 per cent at a mean inspired Ēthrane concentration of 2.62 per cent. The normocarbic values at a mean inspired Ēthane concentration of 3.34 per cent were: spikes, 5.4/min; spike waves 11.0/min; burst suppression 58 per cent.

During *hypocarbia* (Pa_{CO_2} 34 torr or less) cerebral irritability appeared to be increased. For example, in 11 observations made at Pa_{CO_2} 24 torr or less and a mean inspired Ēthrane concentration of 2.6 per cent, the frequency of spikes was 20/min, the frequency of spike waves was 14/min, and the duration of burst suppression was 25 per cent. At a mean inspired Ēthrane concentration of 3.36 per cent the frequency of spikes was reduced to 9/min, the frequency of spike waves increased to 26/min, and isoelectric periods occupied 67 per cent of the record (again, see fig. 4 for comparison).

The CO_2 effect on the EEG is demonstrated in another way in figure 5, where reduction in mean Pa_{CO_2} within an Ēthrane range of 2.5–2.9 per cent in 26 observations produced increased frequencies of spikes and spike waves and increased the amount of suppression. With inspired Ēthrane concentrations of 3 per cent or more, the frequency of spikes decreased but the frequency of spike waves and duration of

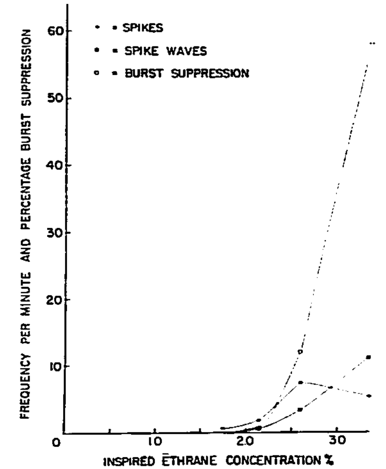

FIG. 4. The frequencies of spikes and spike waves and the percentages of the EEG occupied by burst suppression in 29 EEG's from 14 individuals at four mean Ethrane concentrations at a Pa_{CO_2} range of 35 to 44 torr.

burst suppression increased with reduction of mean Pa_{CO_2}. Little Pa_{CO_2} effect was seen at Ethrane concentrations below 2.5 per cent.

GROUP II

The effects of addition of 60 per cent nitrous oxide to steady-state Ethrane at constant Pa_{CO_2} over an anesthetic range of 1.5–3.4 per cent and a Pa_{CO_2} range of 21–32 torr were evaluated. Prior to nitrous oxide, the EEG pattern was one of light anesthesia in two subjects, spikes without spike waves or suppression in two subjects, and spike waves and suppression in five subjects. In none of these test circumstances did the addition of nitrous oxide alter the predominant EEG pattern.

Discussion

Ethrane can produce profound general anesthesia, as well as EEG patterns and occasional motor movements interpreted as representing cerebral cortical irritability. In this respect it differs from all other clinically used inhalational anesthetics studied to date. Like other halogenated ethers, during light anesthesia (fig. 1) Ethrane has an EEG pattern characterized by frequencies[8, 9] higher than those seen during the administration of diethyl ether[10] and cyclopropane.[11] With methoxyflurane, for example, high-frequency activity may be present as depth of anesthesia increases, but spike forms are not seen.[9] Furthermore, burst suppression appears only at great depths of anesthesia with other halogenated agents.[12, 13] In contrast, spike forms and isoelectric periods are not uncommon with Ethrane under clinical conditions. (MAC for Ethrane–O_2 is approximately 1.68 per cent.[14]) The data indicate that anesthetic depth has more influence than low Pa_{CO_2} in causing the abnormal EEG, although the latter does seem to exert an effect.

We believe that the cerebral irritability that occurs with Ethrane does not pose major problems for the clinician, for the following

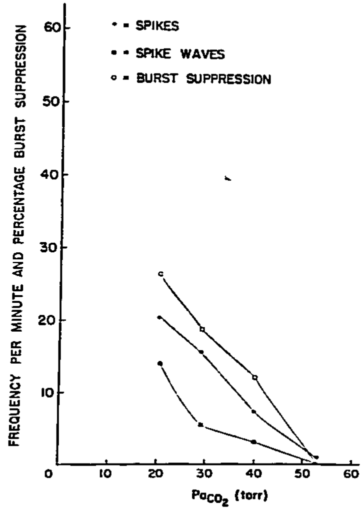

FIG. 5. The frequencies of spikes and spike waves and the percentages of the EEG occupied by burst suppression in 26 EEG's form 11 individuals at four mean Pa_{CO_2}'s at an inspired Ethrane concentration of 2.5–2.9%.

reasons. First, studies of cerebral blood flow, cerebral metabolic rate, and patterns of cerebral carbohydrate metabolism during and after deep Ethrane anesthesia in man have failed to reveal evidence of cerebral hypoxia.[15] Second, behavioral patterns in the immediate and delayed (7–14 day) postoperative[2] or poststudy period[16] have resembled those seen with other inhalational anesthetics. Third, the incidence of abnormal movements in the reported clinical series is low.[1–5] In this study no movements were observed in noncurarized individuals, nor did a multiple-spike seizure pattern occur in the EEG. Fourth, the EEG pattern considered to be indicative of cerebral irritability can be rapidly replaced with a more normal tracing by a reduction in depth of anesthesia.

Anesthetic depth and the modifying effects of Pa_{CO_2} may be readily evaluated by EEG monitoring during Ethrane anesthesia. This will facilitate the changes in inspired concentration and ventilation necessary to protect against significant cerebral irritability.

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