

# The Electroencephalographic Pattern during Anesthesia with Éthrane:

## Effects of Depth of Anesthesia, $P_{aCO_2}$ , and Nitrous Oxide

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The EEG patterns of increasing depths of Éthrane-O<sub>2</sub> anesthesia and the alterations in the patterns produced by changing  $P_{aCO_2}$  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  $P_{aCO_2}$  at which changes occurred have been defined. With elevation of  $P_{aCO_2}$ , indices of cerebral irritability appeared to be reduced, while reduction of  $P_{aCO_2}$  increased their occurrence. The greatest CO<sub>2</sub> effect was seen at inspired Éthrane 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; Éthrane; Carbon dioxide.)

CLINICAL STUDIES OF Éthrane† (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.<sup>1-3</sup> Preliminary data show that the compound undergoes limited biodegradation.<sup>6</sup> The rare occurrence of abnormal motor movements and occasional electroencephalographic (EEG) evidence of cerebral irritability during Éthrane anesthesia have caused concern.<sup>1, 5, 4</sup> 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 Éthrane and the alteration in the EEG produced by changing  $P_{aCO_2}$ . The influence of nitrous oxide on the EEG was also evaluated. Our results indicated that Éthrane 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 Éthrane during elective surgery, and anesthetic and  $P_{aCO_2}$  levels were selected according to standard anesthetic practices. Healthy subjects agreed to the use of Éthrane over a wider range of anesthetic doses and  $P_{aCO_2}$  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 Éthrane (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 Éthrane-O<sub>2</sub> or Éthrane-nitrous oxide-O<sub>2</sub>. 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.

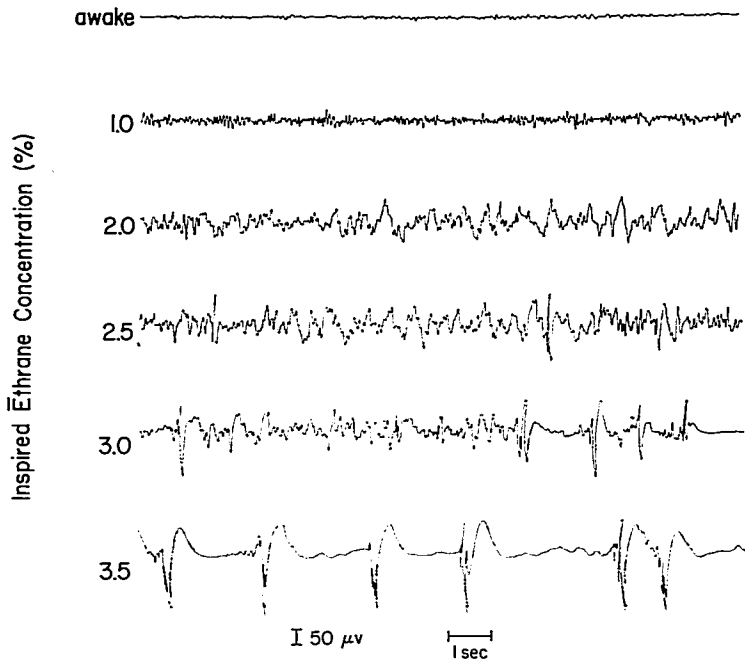


FIG. 1. EEG patterns with increasing depths of Éthrane anesthesia in one subject at  $P_{aCO_2}$  35-39 torr.

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.

Éthrane was administered with a Dräger vaporizer, Copper Kettle, or Éthrane vaporizer manufactured by Cyprane Ltd., in either a nonbreathing 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  $P_{aCO_2}$  desired. Changes in  $P_{aCO_2}$  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. Éthrane concentrations reported are the inspired values when this stable state existed. Arterial blood gases and pH were measured by Instrumentation Laboratory electrodes using procedures and correction factors described elsewhere.<sup>7</sup> Steady-state  $P_{aCO_2}$  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

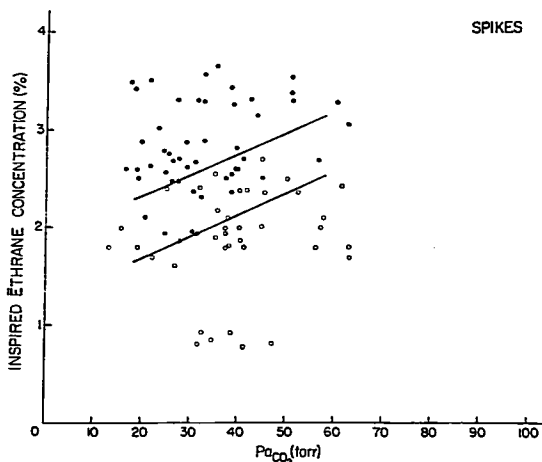


Fig. 2. Spikes of 100  $\mu$ V or more in 80 observations in 21 individuals. Open circles indicate no spike forms. Closed circles indicate one or more spike forms.

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  $P_{aCO_2}$  and were exposed to a variety of stable anesthetic states of Éthane. Nine were maintained at a selected constant Éthane concentration and  $P_{aCO_2}$  was varied. The other four were studied with both: a selected constant  $P_{aCO_2}$  with variation in stable Éthane concentrations was followed by a selected stable Éthane concentration and varied  $P_{aCO_2}$ .

#### GROUP II

Following Éthane-O<sub>2</sub> anesthesia, EEG, anesthetic concentration and  $P_{aCO_2}$  were determined. Nitrous oxide, 3 liters, and oxygen, 2 liters, were then added to the same Éthane concentration at the same  $P_{aCO_2}$  for 20 minutes before EEG, anesthetic concentration, and  $P_{aCO_2}$  were again measured.

### Results

#### GROUP I

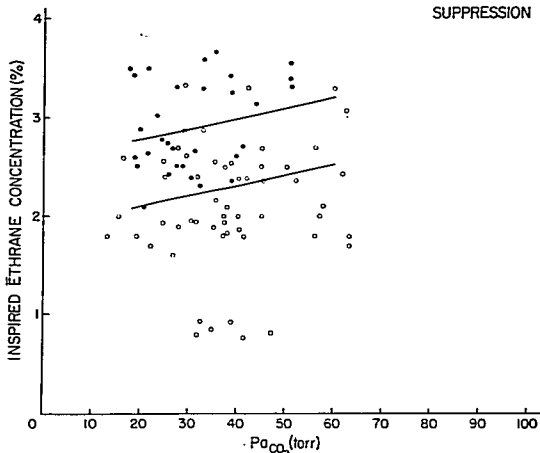
Increasing the depth of Éthane-oxygen was associated with a characteristic change in

the EEG. Figure 1 shows the pattern of the change in one subject at  $P_{aCO_2}$  35-39 torr. As depth increased, spikes (greater than 100  $\mu$ V) 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 Éthane concentration and  $P_{aCO_2}$  was analyzed for the presence or absence of spike forms of 100  $\mu$ V or greater and burst suppression lasting a second or longer. Figure 2 shows the Éthane concentration and  $P_{aCO_2}$  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 Éthane and  $P_{aCO_2}$ . The lines, drawn by eye, separate the zones and indicate the increasing occurrence of spikes with increasing anesthetic depth and decreasing  $P_{aCO_2}$ .

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.



zões was found. Higher Ethrane concentrations were needed to produce suppression and  $P_{aCO_2}$  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 normocarbica ( $P_{aCO_2}$  35–44 torr, fig. 4). As mean Ethrane 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 hypercarbica ( $P_{aCO_2}$  45 torr or more) cerebral irritability appeared to be reduced. At mean inspired Ethrane concentrations of 1.52 and 2.25 per cent, spikes, spike waves and burst suppression did not occur. At a mean inspired Ethrane concentration of 2.6 per cent, the frequency of spikes was 1/min, with neither spike waves nor burst suppression; at a mean inspired Ethrane 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 normocarbica 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 Ethrane concentration of 2.62 per cent. The normocarbica values at a mean inspired Ethrane concentration of 3.34 per cent were: spikes, 5.4/min; spike waves 11.0/min; burst suppression 58 per cent.

During hypocarbica ( $P_{aCO_2}$  34 torr or less) cerebral irritability appeared to be increased. For example, in 11 observations made at  $P_{aCO_2}$  24 torr or less and a mean inspired Ethrane 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 Ethrane 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  $P_{aCO_2}$  within an Ethrane 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 Ethrane concentrations of 3 per cent or more, the frequency of spikes decreased but the frequency of spike waves and duration of

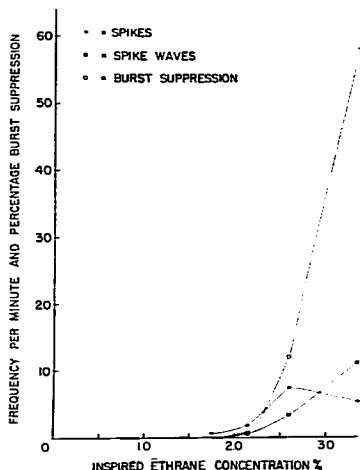


FIG. 4. The frequencies of spikes and spike waves and the percentages of the EEG occupied by burst suppression in 29 EEG's from 14 individuals at four mean Ethrane concentrations at a  $P_{aCO_2}$  range of 35 to 44 torr.

burst suppression increased with reduction of mean  $P_{aCO_2}$ . Little  $P_{aCO_2}$  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  $P_{aCO_2}$  over an anesthetic range of 1.5-3.4 per cent and a  $P_{aCO_2}$  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

Ethane 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<sup>8,9</sup> higher than those seen during the administration of diethyl ether<sup>10</sup> and cyclopropane.<sup>11</sup> With methoxyflurane, for example, high-frequency activity may be present as depth of anesthesia increases, but spike forms are not seen.<sup>9</sup> Furthermore, burst suppression appears only at great depths of anesthesia with other halogenated agents.<sup>12,13</sup> In contrast, spike forms and isoelectric periods are not uncommon with Ethrane under clinical conditions. (MAC for Ethrane-O<sub>2</sub> is approximately 1.68 per cent.<sup>14</sup>) The data indicate that anesthetic depth has more influence than low  $P_{aCO_2}$  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

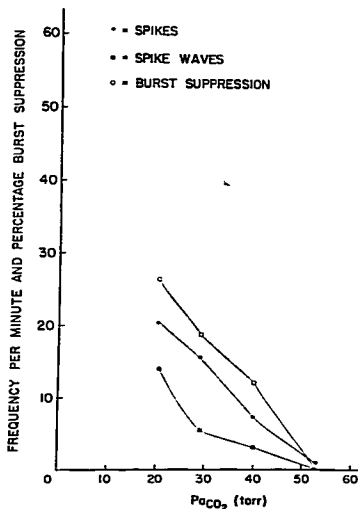


FIG. 5. The frequencies of spikes and spike waves and the percentages of the EEG occupied by burst suppression in 26 EEG's from 11 individuals at four mean  $P_{aCO_2}$ 's at an inspired Ethrane concentration of 2.5-2.9%.

reasons. First, studies of cerebral blood flow, cerebral metabolic rate, and patterns of cerebral carbohydrate metabolism during and after deep Éthane anesthesia in man have failed to reveal evidence of cerebral hypoxia.<sup>15</sup> Second, behavioral patterns in the immediate and delayed (7-14 day) postoperative<sup>2</sup> or poststudy period<sup>16</sup> have resembled those seen with other inhalational anesthetics. Third, the incidence of abnormal movements in the reported clinical series is low.<sup>1-3</sup> 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  $P_{aCO_2}$  may be readily evaluated by EEG monitoring during Éthane anesthesia. This will facilitate the changes in inspired concentration and ventilation necessary to protect against significant cerebral irritability.

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