Ethylene–Halothane Anesthesia:

Addition or Synergism?

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The hydrate microcrystal theory of anesthesia proposed by Pauling and the iceberg hydrate theory proposed by S. L. Miller suggest that simultaneous administration of anesthetics that form different structured hydrates might result in a synergistic anesthetic effect. Using MAC as our potency standard, we determined the anesthetic requirement of man for ethylene (structure I hydrate), halothane (structure II hydrate), and two mixtures of these anesthetics. The results suggest that the administration of halothane and ethylene combined does not produce synergism as predicted by Pauling, but instead produces only a simple additive anesthetic effect. (Key words: Ethylene; Halothane; Theories of anesthesia; MAC; Anesthetic addition; Anesthetic synergism.)

THE HYDRATE MICROCRYSTAL THEORY of anesthesia proposed by Pauling[1] states that inhalation anesthetic agents produce narcosis by the formation of hydrate microcrystals which increase impedance to neuronal transmission, "thus causing the level of electrical activity of the brain to be restricted to that characteristic of anesthesia." In addition, Pauling suggests that a synergistic effect results from administration of inhaled anesthetics that form hydrates with dissimilar structures. Thus, concomitant administration of an anesthetic which forms a structure I hydrate (ethylene) and one which forms a structure II hydrate (halothane) should result in synergism rather than a simple additive anesthetic effect. An alternative, but similar, theory, proposed by S. L. Miller[2] suggested that if the icebergs were large, a synergistic effect would be observed, but if they were small (one gas molecule per iceberg), no synergism would be expected.

The purpose of this study was to test these theories by determining whether simultaneous administration of ethylene and halothane produces addition or synergism. Our results suggest an additive anesthetic effect only.

Methods

Our standard of potency[3] was the minimum alveolar concentration of anesthetic (MAC) required to eliminate gross movement in 50 per cent of patients in response to surgical incision. All subjects studied were healthy 17- to 30-year-old males, 60 to 92 kg in weight, who were undergoing elective herniorrhaphies. The patients received either no medication or atropine sulfate, 0.6 mg subcutaneously, preoperatively. Esophageal temperature was maintained between 35 and 38 C.

The ethylene MAC was determined in 20 patients. The patients breathed 80 volumes per cent ethylene in oxygen at total flow rates greater than 5 l/min. Endotracheal intubation was performed following administration of succinylcholine chloride, 60 mg intrave-

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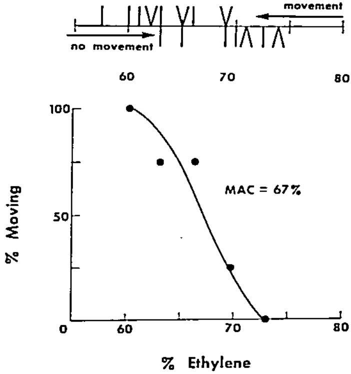


FIG. 1. The upper portion of the graph illustrates the data used to determine the ethylene MAC. If the patient moved in response to a surgical incision, an upward deflection was recorded at the appropriate alveolar concentration. If the patient did not move, a downward deflection was recorded. The data were grouped to arrive at the graph presented in the lower portion of the figure. Starting from the lowest concentration, patients were taken into groups of four. For each group the percentage of those who moved was plotted on the vertical axis, while the alveolar concentration was plotted on the horizontal axis. A visually-determined line was drawn through these points.

nously. Upon recovery from succinylcholine, the patients breathed spontaneously at the desired concentration for 20 minutes. When the desired concentration had been maintained for ten minutes or more, the incision was made. Inspired ethylene concentration was determined indirectly with a Beckman/Pauling D oxygen analyzer, sampling from the inspiratory limb of the circle system. Alveolar ethylene concentration closely approaches inspired concentration after this period of time.[4] The inspired ethylene concentration was calculated by subtracting the oxygen reading from 100 per cent. The alveolar concentration equalled this figure times 0.94, 0.94 correcting for water vapor dilution. The analyzer was calibrated with known concentrations of ethylene.

We determined the halothane end-tidal concentrations with a Mayo Vapor Analyzer. This analyzer was calibrated using known concentrations of halothane.[5] The halothane MAC was determined in 16 patients as described by Saidman *et al.*[3]

MAC in those patients receiving both halothane and ethylene was determined as follows. Anesthesia was induced with halothane and oxygen at total flows exceeding 5 l/min. Following endotracheal intubation ethylene was added to the inspired gas. Predetermined levels of end-tidal halothane and inspired ethylene concentrations were established and maintained for at least 15 minutes prior to incision of the skin.

The anesthetic combinations studied were: ethylene and halothane, each at ½ MAC, in a group of 16 patients; and ethylene at ¼ MAC plus halothane at about ¾ MAC in a second group of 12 patients. Individuals in both groups were held at alveolar halothane concentrations both above and below the concentration at which 50 per cent of the patients moved in response to incision of the skin. For any particular subject the alveolar concentrations of ethylene and halothane were divided

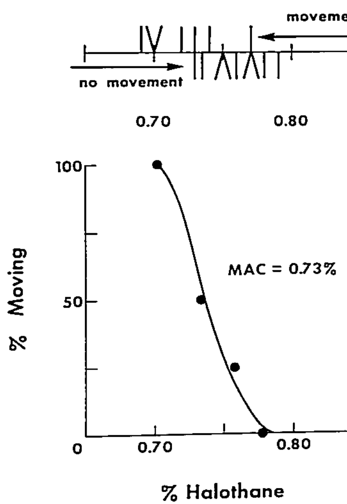


FIG. 2. Data used to determine halothane MAC (see legend to figure 1).

FIG. 3*A* and *B*. Method of determination of the combined "MAC." These are identical to figures 1 and 2 except that the horizontal axes represent

$$\frac{\text{alveolar ethylene}}{\text{ethylene MAC}} + \frac{\text{alveolar halothane}}{\text{halothane MAC}}$$

obtained from each subject.

by their respective MAC values and these figures added[2]:

Combined normalized "MAC"

$$= \frac{\text{alveolar ethylene}}{\text{ethylene MAC}} + \frac{\text{alveolar halothane}}{\text{halothane MAC}}$$

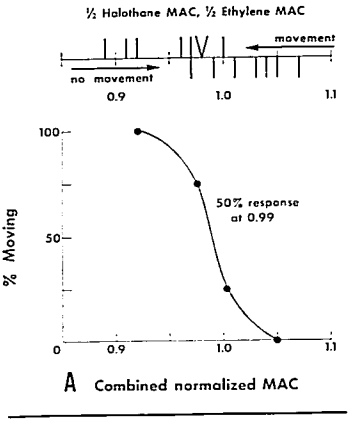
These data were then plotted as in the previous MAC studies. A combined normalized "MAC" of less than 1 would indicate synergism, while a combination equal to 1 would indicate simple addition of anesthetic effect.

Results

No patient moved at a concentration greater than 69 per cent ethylene, while all patients moved at concentrations below 63 per cent ethylene. The MAC for ethylene was 67 per cent (fig. 1).

In the determination of MAC for halothane, only one patient moved at a concentration above 0.74 per cent. All patients moved at concentrations below 0.73 per cent halothane (fig. 2). The resultant MAC for halothane was 0.73, which is in close agreement with that found by Saidman *et al.* for an older age group (30–55 years).[3]

The administration of ethylene and halothane, combined, produced an additive anesthetic effect. The combined normalized "MAC" for ½ MAC ethylene and ½ MAC halothane



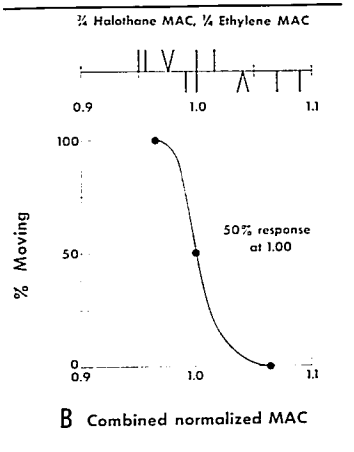


TABLE 1.

	Halothane	Ethylene	½ MAC Halothane; ½ MAC Ethylene	¾ MAC Halothane; ¼ MAC Ethylene
Number of subjects	16	20	16	12
Age (years)	20.6 ± 4*	23.1 ± 5	20.7 ± 4	20.5 ± 3
Time from induction to incision (min)	98 ± 37	22 ± 2	83 ± 28	88 ± 22
Time stable prior to incision (min)	36 ± 19	13 ± 3	28 ± 11	31 ± 10

* Standard deviation.

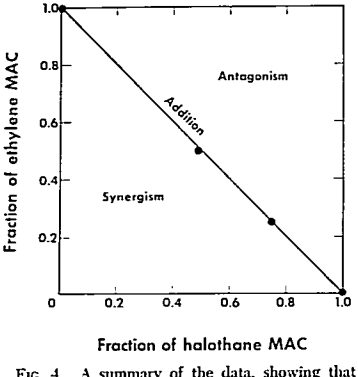


FIG. 4. A summary of the data, showing that neither synergism nor antagonism was found. The vertical axis is the fraction of the ethylene MAC, that is, a value of 1.0 is 1.0 MAC or 67 per cent ethylene. Similarly, the horizontal axis is the fraction of the halothane MAC where 1.0 is 1.0 MAC or 0.73 per cent halothane. The straight line connecting the 1.0 points is described by the equation: (alveolar ethylene/ethylene MAC) + (alveolar halothane/halothane MAC) = 1, and is the line of simple addition of anesthetic effect. The alveolar ethylene and halothane concentrations are those combined concentrations preventing movement in 50 per cent of patients. The points obtained in this study fall on the line of simple addition. Synergism would have been shown by a position below the line (combined normalized "MAC" less than 1), while antagonism or competition for anesthetics sites would be shown by a position above the line (combined normalized "MAC" greater than 1).

was 0.99 (fig. 3A). The combined normalized "MAC" for ¼ MAC ethylene and ¾ MAC halothane was 1.00 (fig. 3B).

Table 1 demonstrates some of the data and shows that there were no significant differences among the various groups except in time from induction to incision in the ethylene studies.

Discussion

Our data show that simultaneous administration of halothane and ethylene, which form hydrates with different structures, results in an additive anesthetic effect (fig. 4). Within the framework of Pauling's theory[1] these data show that the microcrystals must be smaller than he originally estimated. Within the framework of Miller's theory[2] these data show that the icebergs must act independently, that is, that only one anesthetic molecule is in each iceberg. The data are consistent with a lipid solubility theory.

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