

Observations on the Anesthetic Effect of the Combination of Xenon and Halothane

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In their descriptions of the hydrate theory of anesthetic action Pauling and Miller suggested that the action of two anesthetic gases might be synergistic if one gas formed a structure I and the other a structure II hydrate. The correlation of anesthetic potency and lipid solubility, however, suggests that combinations of anesthetics should result in an additive effect rather than synergism. We compared the anesthetic requirements, as defined by MAC, for xenon (structure I hydrate) and for halothane (structure II hydrate) with MAC values for xenon-halothane mixtures in man. The results indicate that xenon and halothane in combination have an additive rather than a synergistic anesthetic effect. (Key words: Xenon; Halothane; Theories of anesthesia; MAC; Anesthetic addition; Anesthetic synergism.)

THE HYDRATE THEORIES of Pauling¹ and Miller² suggest that anesthetic agents of dissimilar structure may act synergistically. Pauling stated, "It is known that two anesthetic agents can cooperate to increase the stability of the hydrate framework." Miller suggested as a remote possibility that the molecules which form structure I hydrates^{3*} (such as those formed by xenon) and those which form structure II hydrates (such as those formed by the larger molecule, halothane) might act synergistically. The sites of action of the two

anesthetics would have to be interdependent for this to occur. No synergism would be expected if the sites were independent (*i.e.*, if the icebergs were not immediately adjacent).³ Synergism here means that the effect of the combination is greater than the sum of the effects of the individual agents.

In contrast to the above prediction of synergism, the correlation of lipid solubility and anesthetic potency suggests that the combination of agents produces only an additive effect. This correlation suggests that anesthesia is achieved by the presence of a critical number of anesthetic molecules of any kind at the lipid or lipid-like site of anesthetic action, that is, it does not matter what molecules are present, but rather how many. Note that this is not a detailed molecular explanation of anesthesia. It does not identify the lipid phase, nor does it suggest that anesthetics must act in a lipid phase: a hydrophobic protein phase might be equally suitable.

Prior to the inquiry reported here, no detailed testing of the postulates pertaining to synergism as opposed to addition of anesthetic effect has been undertaken. MAC, or minimum alveolar concentration of anesthetic required to eliminate gross movement in 50 per cent of patients in response to surgical incision, permits a detailed objective testing of these postulates.⁴

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** A structure I hydrate is a clathrate composed of a gas encaged in a distorted ice matrix where there are six to ten water molecules for each anesthetic molecule. A structure II hydrate contains a larger cavity for the anesthetic molecule and the ratio of water to anesthetic molecules is 17 to 1. Structure I hydrates can be formed only with the smaller anesthetic molecules; larger anesthetic molecules can form only the larger structure II hydrates.^{1,4}

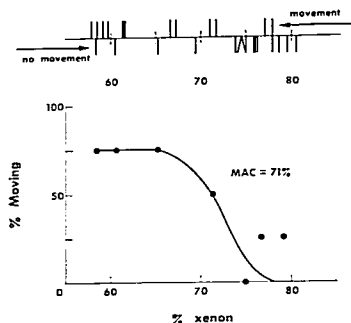


FIG. 1. The upper portion of the graph illustrates the data from which the xenon MAC was derived. Each upward projection from the horizontal line represents a patient who moved with surgical stimulation. The position on the line indicates the alveolar xenon concentration present in the period preceding movement. Similarly, each downward projection represents a patient who did not move, and the associated alveolar concentration. The data were combined to produce the lower graph. The patients were grouped in fours, starting from those who had the highest alveolar xenon concentrations and proceeding downward. The mean alveolar xenon concentration and the mean percentage moving were then plotted as the dotted circles. A visual line of best fit was drawn through these points. The 50 per cent intercept, or 71 per cent xenon, was taken as MAC.

Methods

Xenon and halothane were selected as the agents to be tested. Xenon was chosen because it represents an anesthetic which forms a structure I hydrate; it produces anesthesia in man at less than one atmosphere⁵; it is easily measured in a mixture of gases; and it does not interfere with infrared analyses of halothane. Halothane was chosen because it represents an anesthetic which forms a structure II hydrate, and because the MAC for this agent had been repeatedly measured and found constant in the range between 0.74 and 0.76 per cent.^{4,6,7}

MAC for xenon was established in the standard manner. Following premedication with atropine, usually 0.4 mg, the patient's lungs were denitrogenated for 12 minutes using a circle absorption anesthetic system with inflow rates of oxygen greater than 10 l/min. After 12 minutes, reduction of oxygen inflow to 1

l/min caused no reduction in the inspired oxygen concentration as measured with a Beckman-Pauling model D oxygen analyzer. The system was then closed and the rebreathing bag emptied after a full expiration by the patient. Xenon was then introduced into the closed system and the flows of oxygen and xenon adjusted to achieve the desired percentage.

Following induction of anesthesia with xenon succinylcholine, 100 mg, was administered intravenously to facilitate tracheal intubation. The inspired xenon-oxygen mixture was maintained at a predetermined concentration for 15 or more minutes after intubation. The patient was then observed for movement in response to incision of the skin. Alveolar xenon concentration was determined by subtracting the oxygen concentration in the system during xenon-oxygen breathing from that obtained at the end of the denitrogenation period. Applying the corrections described below, this value was taken as the alveolar xenon concentration. At the end of each study a sample of gas was drawn from the system and analyzed for nitrogen. The concentration of nitrogen was usually less than 1 per cent, and was subtracted from the percentage of inert gas. The percentage of inert gas was also corrected for dilution by water vapor and for the presence of krypton. In 62 per cent of our cases the xenon actually was a mixture of 95 per cent xenon and 5 per cent krypton. In these cases we assumed that the 5 per cent krypton represented about 1.5 per cent xenon in potency and corrected the inert gas concentration for this difference. No difference between results in those receiving pure xenon and those receiving the xenon-krypton mixture was seen.

Patients to be tested with the combination of xenon and halothane underwent induction of anesthesia with halothane in oxygen at inflow rates greater than 5 l/min. Endotracheal intubation was performed and a steady state maintained at the desired level of halothane. After sufficient time for denitrogenation, the system was emptied and then closed, and xenon was admitted. Two combinations of xenon and halothane were tested. In the first xenon was given at about $\frac{1}{2}$ MAC; that is, at an alveolar concentration of about 24 per cent.

Halothane was given at concentrations slightly above or below about $\frac{2}{3}$ MAC in order to develop a range of concentrations at which patients did or did not move in response to incision. In the second combination, xenon was given at $\frac{1}{2}$ MAC and halothane was also given at about $\frac{1}{2}$ MAC, but was varied as in the first combination. End-tidal halothane was measured with an infrared analyzer and inspired xenon was measured as described above. Pure xenon was used for these studies.

The data for the combined anesthetic administrations were analyzed as follows: for any particular subject a combined normalized "MAC" was obtained by adding the alveolar concentrations of xenon and halothane after division by their respective MAC values²:

Combined normalized "MAC"

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

These were then plotted as in the previous MAC studies. If the "MAC" for this added combination were less than 1, this would indi-

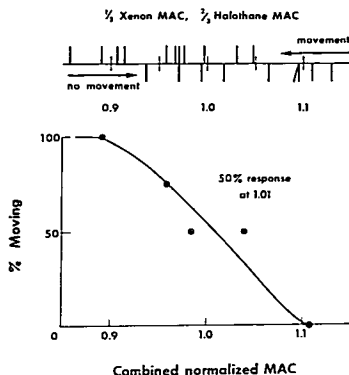


FIG. 2. Illustration of the technique used to calculate the combined normalized "MAC" of 1.01 for the group in which we administered approximately $\frac{2}{3}$ halothane MAC plus $\frac{1}{2}$ xenon MAC. The technique is identical to that used in the calculation of the xenon MAC (see fig. 1) except that "alveolar concentration" or combined normalized "MAC" is calculated as (alveolar Xe/Xe MAC) plus (alveolar halothane/halothane MAC).

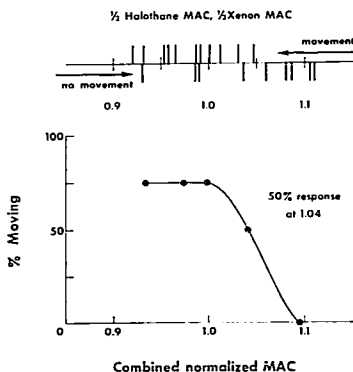


FIG. 3. Data for the group that received $\frac{1}{2}$ halothane MAC and $\frac{1}{2}$ xenon MAC. The combined normalized "MAC" is 1.04.

cate synergism. If the "MAC" for the added combination equalled 1, this would indicate a simple additive anesthetic effect.

Results

MAC for xenon was found to be 71 per cent (fig. 1). It is of historical interest that the MAC obtained under these much better controlled conditions agrees remarkably well with the crude observations made earlier.⁵ MAC for halothane previously was found to be 0.76 per cent.⁷ "MAC" for the combination of xenon and halothane equalled 1.01 for the $\frac{1}{2}$ to $\frac{2}{3}$ combination (fig. 2) and 1.04 for the $\frac{1}{2}$ to $\frac{1}{2}$ combination (fig. 3). These results are summarized in figure 4.

Pertinent data are given in table 1. There was a small but significant temperature difference between the $\frac{1}{2}$ halothane- $\frac{1}{2}$ xenon group and the halothane or xenon group. The time from induction to incision was significantly greater in the group anesthetized with the combinations of xenon and halothane. However, time of xenon anesthesia prior to incision and elapsed time at the test concentration were significantly less in the $\frac{1}{2}$ halothane- $\frac{1}{2}$ xenon group. Last, $(F_I - F_E)/F_E$ for halothane was significantly greater for $\frac{1}{2}$ halothane- $\frac{1}{2}$ xenon (F_I is the inspired concentration; F_E the end-tidal concentration).

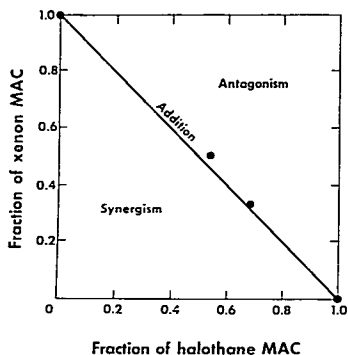


FIG. 4. Summary of the data, showing that

neither synergism nor antagonism was found. The vertical axis is the fraction of the xenon MAC, that is, a value of 1.0 is 1.0 MAC of 71 per cent xenon. Similarly, the horizontal axis is the fraction of the halothane MAC where 1.0 is 1.0 MAC or 0.76 per cent halothane. The straight line connecting the 1.0 points is described by the equation: (alveolar xenon/xenon MAC) + (alveolar halothane/halothane MAC) = 1, and is the line of simple addition of anesthetic effect. The alveolar xenon 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 anesthetic sites would be shown by a position above the line (combined normalized "MAC" greater than 1).

Discussion

Our data demonstrate that the effect of halothane and xenon combined is simply additive. This would be anticipated from the correlation between potency and lipid solubility. Our data do not support Pauling's suggestion that synergism may be produced by the combination of anesthetics which form structure I and structure II hydrates. Our data suggest that if either the hydrate theory¹ or the iceberg theory² is correct, then the icebergs are independent or the microcrystals are smaller than originally suggested by Pauling.

R. Miller and co-workers³ have also found an additive effect from the combination of the structure I and structure II stabilizing anesthetics, ethylene and halothane. It has not been suggested by any of the theories of anesthesia that synergism would be observed with a combination of two structure I-forming anesthetics (such as ethylene and xenon) or two structure II-forming anesthetics (such as halothane and chloroform). Because of this and the evidence we and R. Miller have found, we conclude that all combinations of inhaled anesthetics are probably additive.

We would be remiss if we did not point out possible deficiencies in our data. There is some scatter in the xenon MAC data. However, the xenon MAC is unlikely to be more than 1 to 2 per cent too low, considering that seven patients failed to move between 73.5

TABLE 1.

| | Halothane | Xenon | $\frac{1}{2}$ Halothane; $\frac{1}{2}$ Xenon | $\frac{1}{2}$ Halothane; $\frac{1}{2}$ Xenon |
|---|------------|------------|---|---|
| Number of subjects | 24 | 28 | 20 | 20 |
| Age (years) | 42.1(7.3) | 43.2(17.0) | 41.6(8.2) | 41.3(8.6) |
| Temperature | 36.1(0.4) | 36.1(0.5) | 36.2(0.4) | 36.6(0.5)*† |
| Time from induction to incision (min) | 52(12) | 35(10.3) | 51.7(18.1)*† | 64.8(11.5)*† |
| Time of xenon anesthesia prior to incision (min) | — | 35(10.3) | 31.0(11.3) | 24.3(7.2)† |
| Time at test concentration(s) prior to incision (min) | 27(11) | 28.3(8.9) | 22.8(11.1) | 19.6(7.2)†‡ |
| ($F_I - F_E$)/ F_E for halothane | 0.13(0.06) | — | 0.16(0.08) | 0.18(0.8)§ |

* $P < 0.001$ compared with halothane alone.

† $P < 0.001$ compared with xenon alone.

‡ $P < 0.025$ compared with xenon alone.

§ $P < 0.025$ compared with halothane alone.

Numbers in parentheses are standard deviations.

and 76 per cent. It might be 8 per cent too high—that is, a MAC as low as 63 per cent would be possible. A lower xenon MAC would only enhance the argument against synergism since it would increase the combined MAC further above 1. Even so, this effect would be small, and a xenon MAC of 63 per cent would raise the combined normalized MAC only to 1.06.

The data on which the halothane MAC rests show far less scatter and are supported by results of three previous studies^{4, 6, 7} which agree within a range of 0.02 per cent halothane. It is possible that this value is slightly high because the inspired-to-end-tidal differences were not reduced to zero, but equalled as much as 10 to 20 per cent of the value studied.⁹ We estimate that this might produce, at most, an error of 0.02 to 0.04 per cent halothane. Correction of this error, however, would only raise the combined MAC. On the other hand, the $(F_I - F_E)/F_E$ values for the combinations were higher than for halothane alone (table 1). This might lead to a greater overestimate of the halothane value in the combined groups. However, in the combined groups halothane represented only a fraction of the total anesthetic. The overestimate in the group where halothane was used alone might have been equal though it represented a smaller fraction of the halothane contribution. In any case, these would probably produce only small errors.

Last, the small (0.5 C) but significantly higher body temperature in the group receiving the combination of $\frac{1}{2}$ halothane and $\frac{1}{2}$ xenon might also have influenced our results. If the human MAC is affected by temperature to the same extent as the canine MAC,¹⁰ this should produce an error of about 3 per cent, and may explain the 4 per cent deviation of this group from 1.00.

The above possible inadequacies of the data mean that these studies cannot exclude a small

synergistic effect. However, a reduction in MAC greater than 10 per cent would seem unlikely.

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