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The Minimum Alveolar Concentration of Enflurane in Man

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The minimum alveolar concentration (MAC) of enflurane in man was found to be 1.68 per cent, a value close to that which would have been predicted, based on its lipid solubility.

ENFLURANE (Ethrane ‡) (1-chloro-1,1,2-trifluoroethyl difluoromethyl ether) is a volatile anesthetic that has been under clinical investigation in man for the past three years.[1-4] Advantages of the drug established thus far are rapid, smooth induction and emergence, nonflammability,[2, 3] good muscle relaxation,[1] stable cardiac rhythm,[1] and low incidence of postanesthetic nausea and vomiting.[1]

The most undesirable side-effect is that of excitation of the central nervous system at levels of anesthesia[1, 3] deeper than those needed for most surgical procedures. Since CNS excitation is not seen during light anesthesia, and since enflurane appears to be a promising agent for clinical use, we have attempted to define more precisely the amount of enflurane necessary for light surgical anesthesia by determining the minimum alveolar concentration (MAC) of enflurane in man.

Method

The subjects of the study were 19 surgical patients without evidence of cardiopulmonary disease ranging in age from 20 to 55 years (mean 39). Written consent to receive enflurane was obtained from every patient. After premedication with atropine, 0.4 to 0.6 mg im, anesthesia was induced with enflurane and oxygen. Once an adequate depth of anesthesia had been achieved, the patient was paralyzed with succinylcholine, 1 mg/kg, the trachea and larynx were sprayed with 2 ml of 4 per cent lidocaine, and the trachea was intubated with a cuffed endotracheal tube.

End-expired gas samples were collected through a nylon catheter passed to the tracheal end of the orotracheal tube and were monitored continuously with a Beckman Model LB-1 infrared halothane analyzer for which an enflurane calibration curve had been prepared as previously described.[5] Analysis was performed at ambient pressure and zero flow through the analyzer. The nasopharyngeal temperature was measured and the EKG monitored in every patient.

Anesthesia was progressively deepened until the end-expired enflurane concentration equalled 1.42 to 2.1 per cent and then held constant by adjusting the inspired concentration. The end-tidal concentration in each patient was kept constant for 15 to 51 minutes to allow equilibration of the brain with the alveolar anesthetic partial pressures.[6]

Respirations were assisted when they were too rapid or too shallow to permit easy sampling of end-tidal gas. At the time of incision, the patient was observed for movement, the end-tidal enflurane concentration noted, and the accuracy of the analyzer tested once more with the calibrating tanks. In ten patients, inspired concentration was measured at the time of incision of the skin also.

MAC was determined as in previous studies.[6-8] Patients are taken in groups of four, starting with those tested at the lowest alveolar concentration. The percentage of patients moving within each group is plotted against the group's average alveolar enflurane concentration. That alveolar concentration at which 50 per cent of patients moved represents MAC for the agent being studied.

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‡ Ethrane is a trademark of Ohio Medical Products, a Division of Air Reduction Company, Inc.

TABLE 1. Data Obtained in the Enflurane MAC Determinations

Patient	Total Minutes Enflurane*	Minutes at Test Concentration†	F_E‡	F_I§	$\frac{(F_I - F_E)}{F_E} \times 100$	Movement	Temperature (C)	Age (years)
1	37	22	1.75			Yes	37	20
2	57	51	1.9			No	35.8	23
3	27	16	2.0			No	36.5	50
4	29	19	1.75			No	36	55
5	30	15	1.72			Yes	35.4	41
6	36	26	2.07			No	35.9	49
7	55	38	1.7			Yes	35.8	49
8	30	15	1.85			No	36.2	51
9	45	26	1.82			No	36.9	49
10	30	17	1.72	2.0	16	No	36.5	29
11	26	15	1.63	2.1	29	No	36.1	48
12	59	38	1.66	2.15	29	No	36	38
13	37	24	1.55	2.08	34	Yes	36	22
14	46	20	1.42	1.66	17	Yes	36.1	22
15	41	26	1.55	1.95	27	Yes	36.2	24
16	33	17	1.65	1.85	12	Yes	36.2	48
17	32	15	1.70	1.88	12	No	36.4	49
18	21	15	1.44	1.85	28	Yes	36.2	49
19	27	15	1.65	1.90	15	Yes		23

* Total duration of enflurance administration prior to incision.
† Total duration of end-tidal concentration at time of incision.
‡ End-tidal enflurane concentration immediately prior to incision.
§ Inspired enflurane concentration immediately prior to incision.

Results

The data obtained from the patients studied are listed in table 1, and individual responses to incisions of the skin are shown in figure 1. All patients moved at alveolar concentrations less than 1.63 per cent, and no patient moved at concentrations greater than 1.75 per cent. MAC for enflurane was found to equal 1.68 per cent (fig. 2).

Discussion

Several possible correction factors may be applied to our results. First, the ages of our patients ranged from 20 to 55 years. Previous studies have shown that MAC for halothane may vary with age, decreasing from 1.08 per cent in infants to 0.92, 0.84, 0.76, and 0.64 per cent at 15, 24, 42, and 81 years of age, respectively.[9] If the same relationship held

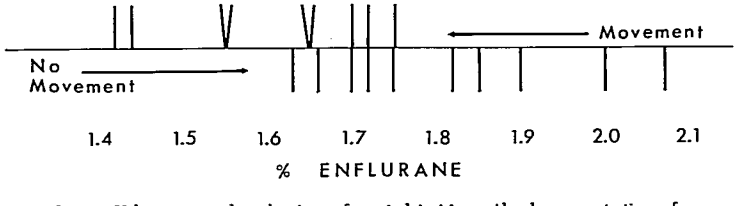

FIG. 1. Values measured at the times of surgical incision. Alveolar concentrations of enflurane are plotted on the horizontal axis. A positive response (movement when the skin was incised) is noted by an upward deflection, and a negative response by a downward deflection.

true for enflurane, we would expect MAC to increase from 1.68 per cent in our group (mean age 39) to 1.90 per cent in young adults, and to decrease to less than 1.55 per cent in those patients more than 70 years old.

Second, the possibility exists that the alveolar anesthetic partial pressure does not accurately reflect arterial, and hence brain, partial pressure. Eger *et al.*[10] demonstrated alveolar–arterial anesthetic partial pressure differences in man as well as animals, because of a difference between partial pressures in inspired and end-tidal gas. Presumably, end-tidal gas is contaminated by inspired gas, which produces a difference between true alveolar gas (gas from well-perfused alveoli) and that gas returning from alveoli that are ventilated but inadequately perfused (deadspace gas). The greater the inspired-to-true alveolar difference, the greater the effect of such contamination on the measured alveolar (end-tidal) concentration.

Enflurane, with a blood/gas partition coefficient of 1.90,[1] is only moderately soluble in blood. As a result, uptake of anesthetic, and hence the inspired concentration, decreases rapidly as the highly perfused tissues are saturated. In those patients in whom inspired concentration was measured, it was not greater than 34 per cent more than the measured end-tidal concentration (mean 22 per cent) at any time. In this case, even with as much as 10 per cent contamination of alveolar with inspired gas, the measured end-tidal partial pressure would be less than 5 per cent higher than true alveolar partial pressure.

Our patients received no premedication except atropine, and no nitrous oxide was used. Previous studies,[6, 7] have shown that premedication with morphine, 8–15 mg, lowered MAC values for halothane and fluroxene by 7 and 20 per cent, respectively. Adding 70 per cent N_2O to halothane,[7] 77 per cent to fluroxene,[6] and 60 per cent to methoxyflurane[11] reduced MAC's 61, 76, and 56 per cent, respectively. Therefore, we might assume that 70 per cent N_2O would lower enflurane MAC to about a third of the initial value, or approximately 0.56 per cent.

Other studies have shown a correlation between MAC and the oil/gas partition coefficient of an anesthetic[6-8, 12, 13] such that the mean of products of oil/gas partition coefficient times MAC for all anesthetics can be used to predict MAC for any new anesthetic. This value (148 for all agents so tested) divided by an enflurane oil/gas partition coefficient of 95 gives a predicted enflurane MAC of 1.55—close to what was actually found.

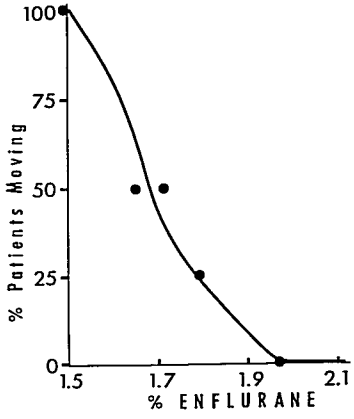

FIG. 2. MAC determined from data in figure 1. Starting with the lowest concentrations, subjects were taken in groups of four, and the percentage of patients within each group that moved was plotted against the group's mean end-tidal enflurane concentration. MAC is that enflurane concentration where a line connecting the individual points passes through the 50 per cent point.

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Metabolism

PSEUDOCHOLINESTERASE LEVELS AFTER BODY BURN Cholinesterase and pseudocholinesterase levels in the erythrocytes of 69 persons who had suffered extensive body burns were determined at intervals. The normal levels in the authors' laboratory are 2.3–4.0 I.U. for cholinesterase and 2.5–5.0 I.U. for pseudocholinesterase. Thirty-seven patients with an average burn surface area of 23 per cent survived, while 22 who died had an average burn surface area of 56 per cent. Seven patients had been exposed to organic phosphorus compounds at the time of their burns; of these, only one survived. In the survivors, the average pseudocholinesterase level started at 3.6 I.U., fell below 2.0 by the fourth post-burn day, reached a low of 1.4 on the twelfth post-burn day, and returned to 2.0 I.U. by the sixteenth day. In the patients who died, the average pseudocholinesterase level started at 2.0 I.U., fell 1.0 I.U. on the fifth day, and continued to decline to 0.5 I.U. or less by the sixteenth day. Signs and symptoms observed with the low pseudocholinesterase levels (1.0 I.U. or less) included confusion, blurred vision, generalized muscle twitching and weakness, increased tracheobronchial secretions, bronchoconstriction, respiratory muscle weakness, dyspnea, and cyanosis. The mechanism of death in the burned patient with cholinesterase depletion appeared to be primarily one of respiratory failure, often associated with pleural effusions. Treatment of the low pseudocholinesterase states consisted of the administration of blood stored for less than 24 hours. (*Price, W. R., and others: Enzyme Depletion in Major Thermal Burns, Amer. J. Surg. 120: 671–675, 1970.*) EDITOR'S COMMENT: It is of interest to contemplate the possible relationship between these findings and the use of muscle relaxants in similar patients. For example, do we know what happens to pseudocholinesterase levels after massive transfusion with blood stored for more than 24 hours? Parenthetically, one can only express surprise at the largesse exhibited by these authors in concluding that patients died of respiratory failure without any indication whether an attempt was made to support lung function. It is relevant, however, to include acute hypopseudocholinesteresemia as a source of acute respiratory insufficiency! The more we look, the more we find.