

Minimum Alveolar Concentrations and Oil/Gas Partition Coefficients of Four Anesthetic Isomers

Donald D. Koblin, Ph.D.,* Edmond I. Eger II, M.D.,† Brynne H. Johnson, A.B.,‡
Penelope Collins, A.B.,‡ Marilyn H. Harper, M.D.,§ Ross C. Terrell, Ph.D.,¶
Louise Speers, Ph.D.**

We determined the minimum alveolar concentration (MAC) of four structural isomers having the empirical formula $C_3H_2F_5ClO$ in dogs. MAC for three of the four isomers (including isoflurane and enflurane) ranged from 1.41 to 2.67 (volumes per cent at one atmosphere pressure). The olive oil/gas partition coefficients at 37° C for these isomers ranged from 90.8 to 96.6. In contrast, MAC for the fourth isomer, compound 485, was 12.53 per cent atm. However, the oil/gas partition coefficient for that compound was 25.8. These results suggest that isomer 485, despite its high MAC, does not deviate strikingly from the established correlation between anesthetic potency and lipid solubility. (Key words: Anesthetics, volatile: enflurane; isoflurane. Potency, anesthetic: MAC. Structure, molecular. Theories of anesthesia: lipid solubility.)

THE PRODUCT OF MAC and the oil/gas partition coefficient varies by less than three-fold over a 74,300-fold difference in anesthetic potency.¹⁻³ That is, in dogs, the MAC of an agent multiplied by its oil/gas partition coefficient is essentially a constant, 2.1.^{3,4} This close correlation between lipid solubility and anesthetic potency of inhaled agents suggests that these anesthetics act at a hydrophobic site in the central nervous system.¹⁻³

Minor deviations from this correlation do exist. Of particular interest are those provided by isomers, since isomeric compounds usually have similar physical properties, such as lipid solubility. For example, enflurane and isoflurane (fig. 1) are structural isomers, each having a reported olive oil/gas partition coefficient of 98.^{5,6} However, the MAC value for isoflurane

in humans is approximately 1.15 per cent atm,⁷ whereas that for enflurane is 1.68 per cent atm.⁸ These differences in anesthetic requirements for agents having similar oil/gas partition coefficients suggest that the potency of an agent may depend upon factors other than lipid solubility. Any large deviation in the correlation between lipid solubility and anesthetic potency would seriously compromise theories of anesthesia based on hydrophobicity. Initial screening studies in mice demonstrated another isomer of isoflurane and enflurane, compound 485 (fig. 1), to be a relatively poor anesthetic⁹ (as measured by induction time of anesthesia in mice). Therefore, we measured the anesthetic potency of compound 485 with greater precision in dogs, and determined the oil/gas partition coefficient for this agent.

In addition, we measured the anesthetic potency and partitioning properties of a fourth structural isomer, one synthesized by Hoechst, and hence designated as the Hoechst compound (fig. 1). Finally, we redetermined MAC and partitioning values for enflurane and isoflurane.

Materials and Methods

MEASUREMENT OF PARTITION COEFFICIENTS

Oil/gas and water/gas partition coefficients for anesthetic agents were determined using a set of Erlenmeyer flasks having rubber stoppers and a volume of about 2000 ml. Exact volumes were measured by water displacement. The surface of the stopper was covered with aluminum foil to prevent absorption of the anesthetic. A 16-gauge needle was passed through the stopper and foil and attached to a 3-way stopcock. For determination of oil/gas partition coefficients, olive oil (approximately 200 ml) was added to each of the flasks. After the stoppers were put in place and the flasks evacuated of air, 1.00 ml of anesthetic was added. The exact volume of olive oil was determined by weighing the flasks before and then after addition of the oil (density of the olive oil was 0.911 g/ml at 37° C). Each flask was shaken vigorously for approximately 30 s and placed in a water bath at 37° C. Flasks were again shaken 15, 30, and 45 min after introduction of the anesthetic. One or two flasks con-

* Assistant Research Chemist.

† Professor of Anesthesia.

‡ Staff Research Associate.

§ Assistant Clinical Professor of Anesthesia.

¶ Manager, Chemical Products Development, Ohio Medical Products.

** Senior Chemist, Ohio Medical Products.

Received from the Department of Anesthesia, University of California, San Francisco, California 94143, and from Ohio Medical Products, Inc., Murray Hill, New Providence, New Jersey 07974. Accepted for publication October 4, 1980, Supported in part by NIH Anesthesia Research Center Grant GM 15571 and the Anesthesia Research Foundation. Presented at the Annual Meeting of the American Society of Anesthesiologists, St. Louis, Missouri, October, 1980.

Address reprint requests to Dr. Koblin: Department of Anesthesia, University of California, San Francisco, Room 1386 HSE, San Francisco, California 94143.

taining 100 μ l of the anesthetic but no olive oil were included with each run for standard concentrations. At 45 min, the concentration in the gas phase overlying the olive oil was determined by gas chromatography. By knowing the volume of anesthetic injected (V_A , in ml of vapor), the concentration in the gas phase (C_G), the volume of the gas phase (V_G), and the volume of the oil (V_O), the oil/gas partition coefficient [$\lambda = (\text{concentration in oil})/(\text{concentration in gas})$] could be calculated as:

$$\lambda = (V_A - V_G C_G)/(V_O C_G)$$

Water/gas coefficients were determined in a similar manner, except that approximately 1000 ml of water was added to each flask and only 100 μ l of liquid anesthetic was injected into the flask.

DETERMINATION OF ANESTHETIC REQUIREMENT

A total of 19 mongrel dogs weighing 8.6–24 kg were used in this study. To determine the anesthetic requirements of enflurane ($n = 3$) and isoflurane ($n = 10$), dogs were anesthetized with the appropriate agent in oxygen and their tracheas were intubated. Ventilation was controlled with a volume-limited ventilator (Air-Shields®). A leg vein was cannulated for administration of lactated Ringer's solution with 5 per cent dextrose, and MAC was determined for each animal, as described previously.¹⁰ Esophageal temperature was maintained between 37° and 38° C for all experiments. Samples of end-tidal gas were removed with a glass syringe from a catheter inserted into the endotracheal tube, and concentrations were measured by gas chromatography. Each end-tidal level was held constant for at least 15 min prior to stimulation of each dog, and end-tidal concentrations were measured every 2–3 min.

For determination of anesthetic potencies with compound 485 ($n = 3$) or the Hoechst compound ($n = 3$), dogs breathed oxygen for 1–3 min and were immobilized with succinylcholine (approximately 0.2 mg/kg, iv). Tracheas were intubated, and anesthesia was started and maintained with the anesthetic-oxygen mixture at a low inflow rate (approximately 600 ml/min). This low rate was necessitated by the limited availability of these compounds. MAC for each dog was determined in the standard fashion.

Seven of the ten dogs tested with isoflurane were also examined for depression of isoflurane MAC produced by different concentrations of compound 485. We first determined MAC for isoflurane alone, then added increasing amounts of compound 485 at a low inflow rate and redetermined isoflurane MAC

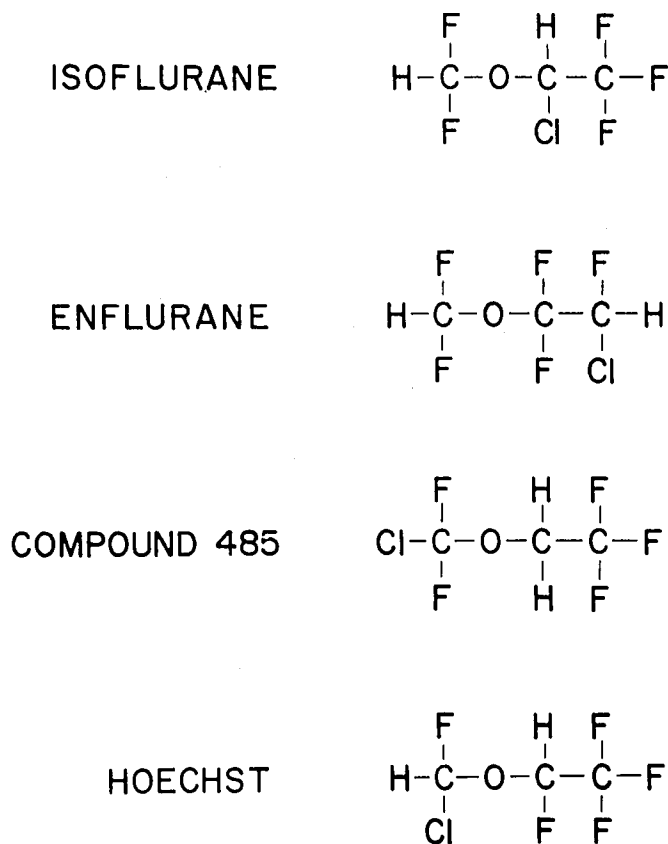


FIG. 1. Each of the four anesthetic isomers having the empirical formula $C_3H_2F_5ClO$ are methyl ethyl ethers. Only one isomer, compound 485, has no hydrogen bonded to an outer carbon.

at stable concentrations of compound 485. Anesthetic concentrations were measured by gas chromatography. Isoflurane and compound 485 were separated with a 360-cm column packed with 10 per cent SF-96 on Chromosorb-WHP,® 60/80 mesh (temperature = 50° C; nitrogen flow = 20 ml/min). High levels of compound 485 resulted in a nonlinear chromatographic response. These concentrations were measured using the required nonlinear calibration curve, or were measured after dilution of end-tidal samples, so that the response of the gas chromatography would be linearly related to the concentration.

Results

MAC values for isoflurane, enflurane, and the Hoechst compound varied by less than a factor of 2, whereas the MAC value for compound 485 was 4.7 to 8.9 times greater than that for the other three isomers (table 1). The addition of compound 485 progressively decreased the fraction of isoflurane MAC required to produce anesthesia (fig. 2), until with no isoflurane present, anesthesia was achieved with com-

TABLE 1. Minimum Alveolar Concentration (MAC) Values (Mean \pm SE) in Dogs and Partition Coefficients of Four Anesthetic Structural Isomers

Anesthetic	MAC* (per cent atm)	MAC Range† (per cent atm)	Oil/Gas Partition Coefficient‡	Water/Gas Partition Coefficient‡	MAC \times Oil/Gas Partition Coefficient
Isoflurane	1.41 \pm 0.06 (10)	1.20–1.71	90.8 \pm 1.0 (6)	0.544 \pm 0.042 (3)	1.28
Enflurane	2.67 \pm 0.14 (3)	2.51–2.95	96.5 \pm 0.6 (3)	0.738 \pm 0.034 (3)	2.58
Compound 485	12.53 \pm 1.20 (3)	10.16–14.00	25.8 \pm 0.1 (3)	0.043 \pm 0.005 (6)	3.23
Hoechst compound	2.24 \pm 0.23 (3)	1.78–2.53	96.6 \pm 0.4 (3)	0.536 \pm 0.004 (3)	2.16

* Number in parentheses indicates the number of dogs examined.
† The range is expressed as low MAC value–high MAC value.

‡ Number in parentheses indicates the number of separate determinations.

Compound 485 alone at a concentration of 12.5 per cent. When compound 485 was given at concentrations from 6 to 12 per cent and isoflurane was not present, convulsions occasionally occurred in dogs. These con-

vulsions were characterized by an arching of the back, an extension of the forelimbs and hindlimbs, and a shaking of the limbs.

For most experiments, end-tidal carbon dioxide levels were between 4 and 6 per cent. However, in the low-flow experiments in which the three dogs were exposed to the Hoechst compound, mixing through the soda lime in the ventilatory system was incomplete, and an elevation in carbon dioxide to 10–15 per cent occurred. For the low-flow studies with compound 485, we were able to improve the mixing in the ventilatory system, and the carbon dioxide levels were normal. At any rate, an increase in end-tidal CO₂ to 10–15 per cent should have little influence on MAC, and if anything, would tend to decrease MAC slightly.¹¹

The oil/gas partition coefficients for isoflurane, enflurane, and the Hoechst compound differed by less than 7 per cent (table 1). The water/gas partition coefficients for these three isomers were similar, varying by less than 40 per cent. However, the oil/gas partition coefficient of compound 485 was 27–28 per cent of the coefficients for the other three agents, and the water/gas partition coefficient for that compound was an order of magnitude lower (table 1).

Discussion

The MAC value we obtained for enflurane (2.67 per cent atm) is similar to the previously reported value of 2.20 per cent atm.¹ Isoflurane MAC in dogs is considerably lower than enflurane MAC (table 1), a finding that is consistent with the relative potencies of these two agents in humans.^{7,8} The MAC for the Hoechst compound fell between MAC values for enflurane and isoflurane. However, compound 485 was 8.9 times less potent than isoflurane (table 1). If the lipid solubility of isoflurane was the same as that of compound 485, this large difference in potencies would seriously compromise theories of anesthesia based on hydrophobicity.

Deviations from the lipid solubility-MAC correlation can be examined by multiplying the MAC of each

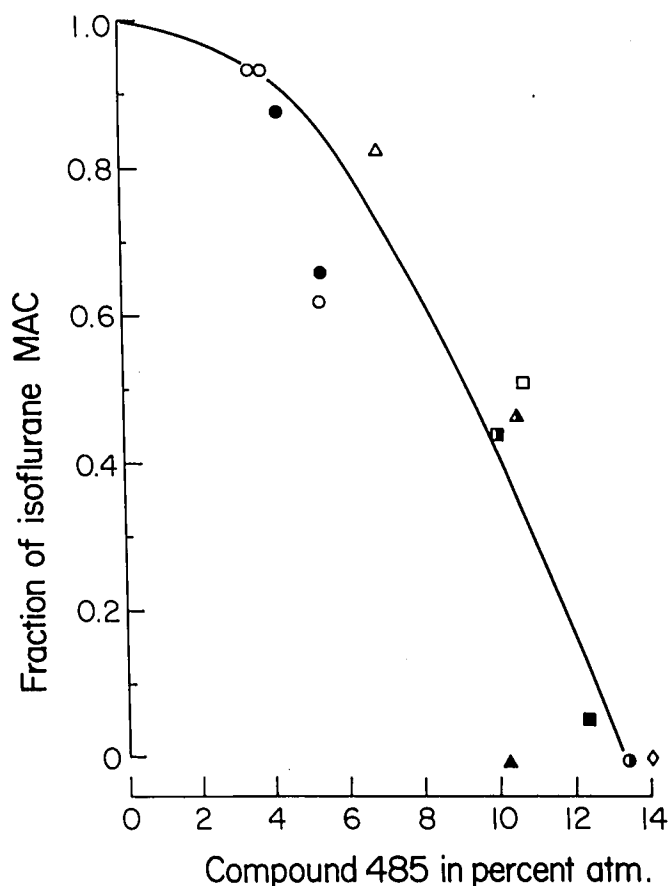


FIG. 2. The fraction of isoflurane MAC required to produce anesthesia decreases in a curvilinear fashion as the concentration of compound 485 increases. Each of the ten symbols represents the results from a different dog. The MAC value for compound 485 in table 1 was calculated from the three dogs that received only compound 485 (symbolized by \blacktriangle , \bullet , and \diamond). The curve represents the best fit of the data to the general expression $y = 1 - ax^2$, where y is the fraction of isoflurane MAC and x is the concentration of 485. Data were fit with a UCLA BMDP statistical program.¹⁴

isomer by its oil/gas partition coefficient (table 1). For a perfect correlation, this product would be the same for all isomers. The product varies from a low value of 1.28 for isoflurane to a high value of 3.23 for compound 485 (table 1). The value for compound 485 is only marginally above the product of MAC and the oil/gas partition coefficient for fluroxene, 2.86, which is the highest value reported for other volatile agents.⁴ We conclude that the 485 isomer does not provide a dramatic exception to the correlation between lipid solubility and anesthetic potency.

Determination of MAC for compound 485 was complicated by the occurrence of occasional convulsions when concentrations of 6–12 per cent of compound 485 were used. Such movement could make it difficult to determine if movement in response to the tail clamp was purposeful. However, we measured MAC between the convulsive episodes, which were usually at least 4 min apart. These convulsions in dogs are consistent with previous reports on mice.⁹ Convulsions induced by compound 485 were not regularly observed when isoflurane at concentrations greater than 0.6 per cent was present. However, because of the limited supply of compound 485, we did not quantitate the amount of isoflurane required to prevent such convulsions.

The addition of compound 485 produced a non-linear decrease in the fraction of isoflurane MAC required to produce anesthesia (fig. 2). The data indicate that the effect of compound 485 and isoflurane may be antagonistic. Such an antagonism might result from the convulsive activity of compound 485. This ability to produce convulsions might explain why compound 485 has a higher MAC value than would be predicted from its lipid solubility, *i.e.*, the convulsive activity may oppose the anesthetic effect. Likewise, MAC values for enflurane (table 1) and fluroxene are higher than predicted, perhaps because these agents are capable of producing convulsions.¹²

The hydrogen atoms of compound 485 are "hidden" on the inside of the molecule, and the end methyl groups of the compound are completely halogenated (fig. 1). In contrast, the three other isomers have at least one hydrogen atom bonded to the end methyl groups (fig. 1). These structural differences between compound 485 and the other isomers apparently ac-

count for the differences in the oil/gas and water/gas partition coefficients. Further insights into the mechanism of how these agents act may be provided by examining the interaction of these isomers with isolated neuronal preparations.¹³

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