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Title : MAC FOR FOUR ANESTHETIC ISOMERS

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Introduction. 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, and has a value of about 2 atm in dogs. This excellent correlation suggests a hydrophobic site of anesthetic action. Any large deviation from the lipid solubility-anesthetic potency correlation would be of considerable theoretical importance since it would seriously compromise the theories of anesthesia based on hydrophobicity. It was therefore of interest to note that initial studies in mice showed that compound 485 (table 1), a structural isomer of enflurane and isoflurane, was a far less potent anesthetic (AD_{50} approximately 10%) and would even produce convulsions.[1] If the isomeric structure resulted in an oil/gas partition coefficient similar to that of enflurane or isoflurane, then compound 485 would represent a significant exception to the correlation of anesthetic potency and lipid solubility. Accordingly, we determined the MAC of compound 485 in the dog, and measured its oil/gas partition coefficient. In addition, we measured the anesthetic potency and partitioning properties of another structural isomer, designated as the Hoechst compound (table 1), and redetermined MAC and partitioning values for enflurane and isoflurane.

Table 1. Four Anesthetic Structural Isomers

Isomer	Structural Formula
Enflurane	CHF_2-O-CF_2-CHFCl
Isoflurane	CHF_2-O-CHCl-CF_3
Compound 485	CF_2Cl-O-CH_2-CF_3
Hoechst compound	CHFCl-O-CHF-CF_3

Methods. MAC was determined according to standard procedures. Three to ten dogs were examined for each anesthetic. Tracheas were intubated and ventilation was controlled with a volume-limited ventilator. A leg vein was cannulated for fluid administration. Esophageal temperature was maintained between 37 and 38 C. End-tidal anesthetic levels were held constant for at least 15 min prior to stimulation. Oil/gas partition coefficients were measured in stoppered Erlenmeyer flasks containing 200 ml of olive oil. Known amounts of liquid anesthetic were added to each flask, and after a 45-min period of equilibration at 37 C, the concentration in the gas phase overlying the olive oil was determined. The partition coefficient was calculated as (concentration in oil)/(concentration in gas). Three to six measurements were performed for each agent. Anesthetic concentrations were measured by gas chromatography.

Results. MAC values for three of the four anesthetic isomers ranged from 1.41 to 2.67% (v/v) atm (table 2). MAC for the fourth isomer, compound 485, was 12.53% atm. The olive oil/gas partition coefficients at 37 C ranged from 90.8 to 96.6 for the three isomers with MACs between 1.41 and 2.67 % atm. In contrast, the olive oil/gas partition coefficient for compound 485 was 25.8 (table 2). In other experiments we showed that the addition of compound 485 progressively decreased the fraction of isoflurane MAC required to produce anesthesia. There appeared to be occasional convulsions with compound 485 at concentrations from 6 to 12% atm when isoflurane was not present.

Table 2. MAC and Oil/Gas Partition Coefficients

Compound	MAC ± SE	Oil/Gas Partition Coefficient (± SE)	(MAC) x (Oil/Gas Partition Coefficient)
Enflurane	2.67±0.14	96.5±0.6	2.58
Isoflurane	1.41±0.06	90.8±1.0	1.28
Compound 485	12.53±1.20	25.8±0.1	3.23
Hoechst compound	2.24±0.23	96.6±0.4	2.16

Discussion. Although compound 485 was much less potent than the other isomers, it also had an oil/gas partition coefficient that was approximately four times lower. The product of MAC and the oil/gas partition coefficient for each of the four isomers ranged from 1.28 for isoflurane to 3.23 for compound 485 (table 2). These are the lowest and highest values of the product of MAC and the oil/gas partition coefficient for all anesthetics examined to date. The two compounds having the highest products (enflurane and compound 485) are both capable of inducing convulsions. This stimulatory capacity of enflurane and compound 485 may indicate an intrinsic anti-anesthetic effect that could explain the higher products found with these agents. We conclude that compound 485 does not provide a dramatic exception to the correlation between lipid solubility and anesthetic potency.

Reference

1. Rudo FG, Krantz JC: Anesthetic molecules. Br J Anaesth 46:181-189, 1974