Halogenation and Anesthetic Potency

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Previous studies have shown that the anesthetic potency of organic compounds increases as a given halogen is replaced with successively larger halogens. These studies often are limited in the accuracy of determination of potency, rarely correlate potency with physical properties, and usually fail to include ether compounds. Because establishing relationships between structure and activity may shed light on anesthetic action, we studied the new anesthetic, I-537 (CHF_2-O-CHBr-CF_3), relative to two other ether anesthetics, I-653 (CHF_2-O-CHF-CF_3) and isoflurane (CHF_2-O-CHCl-CF_3) for both of which MAC and oil/gas partition coefficients are accurately known. The oil/gas partition coefficient of I-537 at 37°C was found to be 245 ± 6 (mean ± SD) and the MAC in Sprague-Dawley rats 0.52 ± 0.07%. Increasing atomic weight of the 1-ethyl halogen (i.e., F in I-653, Cl in isoflurane, and Br in I-537) progressively decreases MAC (increases potency) and increases lipid solubility. Although potency and solubility change by more than 10-fold, the product of MAC and the oil/gas partition coefficient remains essentially constant (120 ± 11). However, this product is significantly less than that for other inhaled anesthetics, a finding which either challenges the unitary theory of narcosis or suggests that the lipid solvent classically used to model the site of anesthetic action (olive oil) is inappropriate.

Key Words: POTENCY, ANESTHETIC—MAC, inhalation anesthetics. ANESTHETICS, VOLATILE—isoflurane, I-653, I-537. THEORIES OF ANESTHETIC ACTION, LIPID SOLUBILITY. PHYSICS, SOLUBILITY.

Structure-activity relationships may provide insights into the mechanisms of anesthetic action. Results from previous studies suggest that halogenation of an organic compound with bromine (Br) produces a more potent anesthetic than halogenation with chlorine (Cl) which, in turn, provides greater potency than fluorine (F) (1,2). Thus, in the CF_3CH_2X series (where X indicates the halogen), substitution of Br for Cl has been reported as increasing potency nearly 3-fold while substitution of Cl for F has been said to increase potency 5-fold (1,2). This relationship also has been reported with other alkane series (Fig. 1).

However, these findings are qualified by: 1) limited accuracy in the determination of anesthetic potency; 2) absence of attempts to correlate potency with physical properties (e.g., important physical characteristics such as lipid solubility are unknown or inadequately defined); and 3) failure to evaluate ether compounds. Only one oil/gas partition coefficient is available for the CF_3-CHFX [namely CF_3-CHFBr (7)] and CF_3-CHClX [namely CF_3-CHClBr (8)] series, and only two are available for the CF_3-CHBrX [CF_3-CHBrF (7) and CF_3-CHBrCl (8)] and CF_3CH_2X [CF_3CH_2F (2) and CF_3CH_2Cl] [Fiserova-Bergerova V, Kawiecki R, unpublished data (9)] series. The noble gases, Ar, Kr, and Xe, are the only series for which all oil/gas partition coefficients have been determined (Table 1).

We have investigated the properties of a new brominated ether anesthetic, (I-537: CHF_2-O-CHBr-CF_3), and compared them to those of two other previously documented ether compounds, one containing chlorine (isoflurane: CHF_2-O-CHCl-CF_3) and the other containing fluorine (I-653: CHF_2-O-CHF-CF_3).

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