

Title : HYDROGEN BOND CHEMICAL SHIFT AND POTENCY OF ANESTHETICS

Authors : S. Yokono, M.D., D.D. Shieh, Ph.D., H. Goto, M.D. and Kasumi Arkawa, M.D.

Affiliation: Department of Anesthesiology, University of Kansas Medical Center, Kansas City, Kansas 66103

Introduction. Anesthetic molecules partitioned in the nerve membrane may form hydrogen bonds with water molecules. The hydrogen bond formation increases the microscopic viscosity of anesthetic molecules, working as a drag force to reduce the momentum of the anesthetic molecules in perturbing the nerve membrane, and may consequently affect their clinical potency. In this report, using proton nuclear magnetic resonance (PMR), the hydrogen bond chemical shifts of four inhalation anesthetics were measured in order to compare the strength of their hydrogen bonds formed with water molecules. It was found that the hydrogen bond chemical shift of anesthetics correlated well with the clinical potencies.

Methods and Materials. Chloroform, halothane, enflurane and isoflurane were used in this experiment. All of them were found to have no impurities by measuring their PMR spectra. The inert solvent, cyclohexane (Eastman spectrograde) was used to disrupt the hydrogen bonds between anesthetic molecules. Methanol (MCB Omni Solv) was used to simulate water. Both form hydrogen bonds with anesthetic molecules.

Various concentrations of the binary mixture of the anesthetic and the solvent were prepared. Proton magnetic resonance (PMR) spectra for each sample were taken on the JEOL FX-100 FT NMR spectrometer at a probe temperature of $37 \pm 0.5^\circ\text{C}$. Tetramethylsilane (TMS) was used as an internal reference for the measurement of proton chemical shift. The successive dilution of each anesthetic caused the hydrogen bonded proton signal of anesthetic to shift upfield in cyclohexane and downfield in methanol. The total hydrogen bond chemical shift of each anesthetic is the sum of the extrapolated chemical shift in the two solvents at the infinitely diluted solution of anesthetics.

Results. PMR hydrogen bond chemical shifts (δppm) of chloroform, halothane, enflurane and isoflurane are listed in Table 1.

Figure 1 shows a good correlation ($r = 0.92$) between the anesthetics' hydrogen bond chemical shifts and their clinical potencies (MAC).

Discussion. A good qualitative correlation between the PMR hydrogen bond chemical shifts with hydrogen bond strength was first reported by Pople, Schneider and Bernstein (1959)¹. Previous data,² expressing the hydrogen bonds strength of chloroform and halothane in thermodynamic parameters and our PMR hydrogen bond chemical shifts of these two anesthetics showed the same trend. Hydrogen bond chemical shifts of the anesthetics can, therefore, be used to compare the hydrogen bond strength.

The good correlation between the total hydrogen bond shifts and the clinical potencies of anesthetics indicates that inhalation anesthetics are less potent if they form stronger hydrogen bonds. It is speculated that the momentum of anesthetic molecules colliding within the hydrophilic part of the membrane is reduced by the hydrogen bonded water. Anesthetic molecules which collide within the hydrophobic part of the membrane must break or weaken their hydrogen bonds

formed with water molecules before they diffuse into that area. In either case, the hydrogen bond formation of anesthetics in water affects the rate of momentum transferred to the nerve membrane. It is thought that the rate of momentum transfer determines the degree of the nerve membrane perturbation in terms of fluidity and disorder. The molecular mechanism of anesthesia probably is related to the nerve membrane fluidization and disorder caused by the constant bombardment of anesthetic molecules. Therefore, the ability in fluidizing and disordering the nerve membrane determine the potency of anesthetics.

Thus, it could be concluded that anesthetics which form stronger hydrogen bonds with water molecules are less potent anesthetics.

References.

1. Pople JA, Schneider WG, Bernstein HJ: High-resolution Nuclear Magnetic Resonance. McGraw-Hill, New York, 1959, pp 400-407
2. Brown JM, Chaloner PA: Strong amide-halothane hydrogen-bonding observed by nuclear magnetic resonance. Can J Chem 55:3380-3383, 1977

TABLE 1
Hydrogen Bond Chemical Shift (δppm)

	Chloro.	Haloth.	Isoflu.	Enflu.
Cyclohexane	0.16	0.14	0.23	0.26
Methanol	0.59	0.92	1.15	1.18
Total shift	0.75	1.06	1.38	1.44

