The Solubility of Methoxyflurane in Human Blood and Tissue Homogenates

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METHOXYFLURANE, a new fluorinated ether anesthetic, is extremely potent yet produces both a slow induction and a slow recovery from anesthesia.[1-8] We now report that these characteristics are related to a high solubility both in oil and in blood. Such solubilities have hitherto not been ascertained, although a water/gas partition coefficient of 4.6 has been calculated[7] from the reported water solubility of 2.2 g. methoxyflurane/100 g. of water at 37° C.[1] The following is a report of the determination of the solubility coefficients in question. Results from studies on tissue homogenates are included.

Method

The technique of Larson *et al.*,[9] with minor modifications,[10] was used to determine partition coefficients. The results are given as Ostwald solubility coefficients (at 37°). These were determined for water, heparinized whole human blood (hemoglobin concentration 14.8 g.), human blood of various dilutions (dilution with distilled water), olive oil (specific gravity at 37° C., 900 g./ml.), homogenized human muscle, grey matter and white matter, and bovine hemoglobin. Tissue specimens were obtained at post-mortem examination (within 12 hours of death) and refrigerated until used. The bovine hemoglobin was found to contain 0.20 g./100 ml. of phospholipid in a solution containing 12 g. of hemoglobin. The effect of this was taken into account in the calculation of the hemoglobin partition coefficient, by assuming a phospholipid partition coefficient of 460 and a specific gravity of 0.9 g./ml. The value thus obtained for hemoglobin was 10 per cent less than the value obtained if the phospholipid content were ignored.

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Results

Results are listed in table 1. The following Ostwald solubility coefficients were found: water 4.50, blood 13.0, oil 825, muscle 17.4, grey matter 22.1, white matter 30.9, and hemoglobin 106. No consistent change in coefficient with concentration was found over the range of concentrations listed although such a change might be predicted from other work.[10-12]

The dilution studies with blood (not listed) showed that the partition coefficient was inversely and linearly related to dilution. For example, when blood and water were mixed 1:1, the coefficient lay halfway between that of blood and that of water.

Discussion

As anticipated, methoxyflurane possesses a high blood coefficient (13.0). This is close to the value obtained for ether (12.1)[10] and in large part explains the slow induction and recovery with methoxyflurane. The low vapor pressure of methoxyflurane also limits rate of induction by limiting the maximal inhaled concentration. The water coefficient of 4.5 is considerably less than that found for ether (13.1).[10] It compares well with the 4.6 value reported previously.[7] The relatively low water coefficient, the dilution studies on blood, and the high hemoglobin coefficient indicate that blood from an anemic patient would give a lower coefficient in the case of methoxyflurane but not in the case of ether which is even more soluble in water than blood.[10, 13, 14] For this and other reasons the anemic (versus the normal) patient would be more easily anesthetized with methoxyflurane.

The oil/gas partition coefficient of 825 is greater than that of any other inhalation anesthetic and establishes methoxyflurane as the most potent anesthetic in use today.[15, 16] From

TABLE 1. Ostwald Solubility or Partition Coefficients of Methoxyflurane at 37° C.

Phases	Number of Determinations	Mean Methoxyflurane Concentration (%)	Range of Concentration	Partition Coefficient ± One Standard Deviation or Range
Water/Gas	8	1.10	(0.32–2.04)	4.50 ± 0.24
Blood/Gas	8	1.36	(0.91–1.83)	13.0 ± 0.5
Oil/Gas	9	0.68	(0.31–1.00)	825.0 ± 58
Muscle/Gas	3	2.34	(2.27–2.40)	17.4 (17.0–18.0)
Grey Matter/Gas	3	1.55	(1.48–1.64)	22.1 (20.8–23.0)
White Matter/Gas	3	1.24	(1.21–1.26)	30.9 (30.6–31.1)
Bovine Hemoglobin/Gas	3	1.25	(1.23–1.27)	106 (98–114)

the ratio of this value to that found for halothane [3] (825/224) it is estimated that methoxyflurane is a little more than three and one-half times as potent as halothane. This is compatible with clinical observation. The minimal alveolar concentration required for halothane anesthesia is about 0.8 per cent, while that for methoxyflurane is about 0.25 per cent—a ratio of 3.2 to 1. (Eger, E. I., II: unpublished data.)

The fat content of adipose tissue is about 60 per cent by volume, the remainder being water and protein.[18] By assuming that the solubility of methoxyflurane in adipose tissue is correspondingly reduced from that of pure fat, an adipose tissue/gas coefficient of 495 (825 × 0.60) is obtained. This provides a fat/blood ratio of 38.1. In experiments by Chenoweth [17] on recovery from methoxyflurane in dogs, a maximum fat/venous blood concentration ratio of between 37 and 41 may be calculated, thus substantially supporting the above analysis.

Solubility of methoxyflurane in tissue is higher than in blood, being 1.34 times greater in muscle, 1.70 times in grey matter, and 2.34 times in white matter. However, relative to blood methoxyflurane is less soluble in the tissues studied than is halothane.[9] This is probably related to the lower oil/blood ratio found with methoxyflurane (63.5 versus 97.4 for halothane). Unlike halothane, solubility of methoxyflurane in brain is greater than in muscle. White matter with its higher lipid content is a better solvent for both anesthetic agents than the low-lipid grey matter. Work by Chenoweth *et al.* substantiates the brain/blood values reported here. Those workers allowed dogs to breathe methoxyflurane for 2½ hours, and at this time determined anesthetic concentrations in venous blood and in various tissues. They found the brain/blood value to vary between 1.41 and 1.94.[17] The correlation with determined *in vivo* muscle solubility was not as good. A muscle/blood value between 0.37 and 0.62 may be calculated from the same study,[17] but it can be assumed that equilibration was not obtained in this more poorly perfused tissue, even at 2½ hours. Although the methoxyflurane tissue/blood values are less than those found with halothane, they exceed the values reported for other anesthetics.[18] Saturation of tissues will thus be correspondingly delayed, and uptake maintained at higher levels than would be expected if the tissue/blood ratio equaled 1 (the more commonly found value).

Summary

Ostwald solubility coefficients of methoxyflurane were determined for various solvents. The values obtained were: for water, 4.50; blood, 13.0; oil, 825; muscle, 17.4; cerebral grey matter, 22.1; cerebral white matter, 30.9; and bovine hemoglobin, 106. These values correlate well with the clinical observation that methoxyflurane is extremely potent yet productive of a slow induction of, and slow recovery from, anesthesia.

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MANNITOL DIURESIS When blood pressure in mammals is lowered, urine flow ceases at a mean arterial pressure of approximately 60 mm. of mercury. This is generally thought to indicate that filtration stops at the hydrostatic pressure in the glomerular capillaries which corresponds to an arterial pressure of 60 mm. of mercury. In experiments on anesthetized dogs and cats, mannitol infusions at a fairly high rate caused urine flow to persist at a reduced rate for long periods after the mean blood pressure had been decreased well below 60 mm. of mercury by bleeding. In animals infused with isotonic saline, urine flow stopped below 50 mm. of mercury, but could be re-established by infusion of hypertonic solutions of mannitol, sodium sulfate, or urea. (*Peters, G., and Grunner, H.: Mannitol Diuresis in Hemorrhagic Hypotension, Amer. J. Physiol. 204: 555 (Apr.) 1963.*)