

Solubility of Fluoroxene in Blood and Tissue Homogenates

Edwin S. Munson, M.D., Lawrence J. Saidman, M.D.,
Edmond I. Eger, II, M.D.

Solubility of fluoroxene was determined in various media. Partition coefficients at 37°C. were: water/gas 0.84, blood/gas 1.37, olive oil/gas 47.7, cerebral grey or white matter/gas 1.96, liver/gas 1.88, and muscle/gas 3.11. Reduction in temperature increased solubility in both water and oil by 5 per cent per degree centigrade. The solubilities obtained correlate well with the clinical finding that fluoroxene is a potent anesthetic with a rapid onset of anesthesia and recovery.

FLUOROXENE (trifluoroethyl vinyl ether) was made available for clinical anesthesia in 1961. Since its initial evaluation in 1953,¹ there have been numerous reports on the pharmacological properties^{2, 3, 4} and the extent of flammability.^{5, 6} However, there is in general a lack of information concerning the physical characteristics of fluoroxene, particularly the solubility coefficients. Lacking this information, one cannot intelligently understand or predict the course of uptake and distribution of fluoroxene. This study was undertaken to determine the solubility of fluoroxene in water, blood, oil, and tissue homogenates.

Method

The technique of Larson *et al.*⁷ with minor modifications was used to determine partition coefficients of fluoroxene in water, olive oil, human blood, cerebral grey and white matter, liver, and skeletal muscle. ACD human blood was obtained from the blood bank and compatible types were pooled. Hematocrit values

were 45. Human tissues were obtained at post-mortem examination, in most cases within 24 hours after death. All tissues had been refrigerated at 5° C. prior to necropsy and were kept refrigerated until the solubility studies were performed. Homogenates were made after gross dissection to free them of fibrous and connective tissue.

All determinations were made with the Beckman infrared halothane analyzer which is also sensitive to fluoroxene. The infrared head was filled with carbon dioxide and a few drops of water to eliminate cross-over effects. Various aliquots of fluoroxene (0.05–0.2 ml.) were injected into two-liter flasks filled with air. Resulting concentrations were calculated from the gas laws and the analyzer calibrated against these concentrations. Prior to each determination, the infrared analyzer was recalibrated against the contents both from a flask and a tank of known fluoroxene concentration. All gases measured were saturated with water vapor and measurements made at 37° C. Determinations were done in triplicate or quadruplicate.

Partition coefficients for fluoroxene in water and olive oil were also determined at temperatures as low as 25° C.

Results

Results are listed in table 1. The following partition coefficients (at 37° C.) were found: water/gas 0.84, blood/gas 1.37, olive oil/gas 47.7, grey or white matter/gas 1.96, liver/gas 1.88, and muscle/gas 3.11.

Partition coefficients for fluoroxene in water and oil at decreased temperatures are shown in figure 1. Values represent means from quadruplicate determinations.

Accepted for publication March 12, 1964. The authors are in the Department of Anesthesia, University of California, San Francisco Medical Center, San Francisco, California. Supported in part by United States Public Health Service grants 5T1-GM-63-06; 5-K3-GM-17, 685-03; and HE 07946-01.

Discussion

Fluroxene displays a relatively low blood/gas partition coefficient (1.37). This value agrees with that reported by Lowe,⁸ who found a blood/gas coefficient of 1.55 by gas chromatographic methods. From this one can predict a rapid onset and recovery from anesthesia. During induction, the rate of rise of the alveolar toward the inspired tension would be intermediate between cyclopropane and halothane. This correlates well with clinical studies which report a rapid induction of anesthesia with fluroxene.^{3,4}

Anesthetic potency may be related inversely to the tension of anesthetic in the brain required to produce anesthesia; *i.e.*, the lower the tension, the greater the potency. Brain and alveolar tensions are essentially in equilibrium soon after induction. Anesthetic potency has been correlated with the oil/gas partition coefficient.^{9,10} This concept may be used to predict relative anesthetic potency. Compared to diethyl ether, fluroxene is slightly less potent (47.7/64.8),¹¹ but four times more potent than cyclopropane (47.7/11.2).¹² The minimum alveolar anesthetic concentration of halothane has been found to be 0.74 per cent.¹³ Applying this concept of relative potency, the minimal anesthetic alveolar concentration of fluroxene can be calculated to be 3.5 per cent ($0.74 \times 224/47.7$).⁷

Reduction in temperature increased the solubility coefficient in both water and olive oil about 5 per cent per degree centigrade. Krantz¹ reported an oil (corn)/water coefficient of 94 at 25° C. Projecting our data to 25° C. (fig. 1), we calculate an oil/water

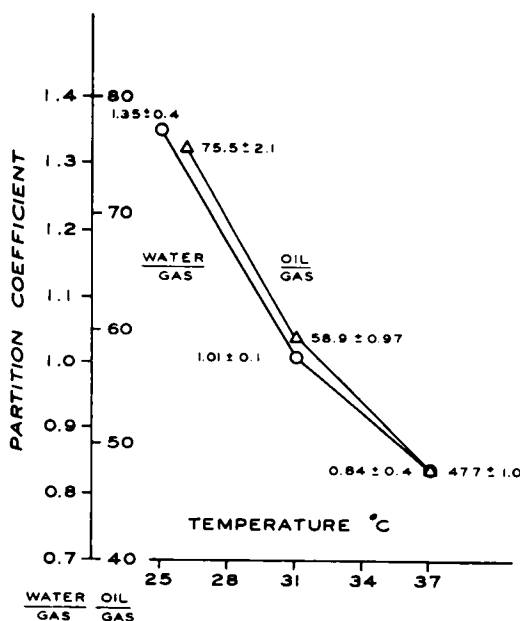


FIG. 1. Effect of temperature on water/gas and oil/gas partition coefficients.

coefficient at 60 (*i.e.*, 80/1.35). This phenomenon of increased solubility at lower temperatures may explain the observations of decreased anesthetic tensions during hypothermia. Thus at 31° C. we would predict that fluroxene would be about 23 per cent more potent than at 37° C. This follows from this comparison of the oil/gas partition coefficients: $58.9/47.7 = 1.23$ (*i.e.*, 58.9 is 23 per cent greater than 47.7). It is probable that increased solubility also occurs in body fluids and tissues during hypothermia.

We believe that the large S.D. for the muscle/gas coefficient determinations (3.11 ± 1.08) represents a biological variation in fat and connective tissue in the specimens rather than an inconsistency in our technique.

Summary

Solubility of fluroxene was determined at 37° C. in water, olive oil, human blood, and various tissue homogenates. Partition coefficients obtained were: water/gas 0.84, blood/gas 1.37, olive oil/gas 47.7, grey and white matter/gas 1.96, liver/gas 1.88, and muscle/gas 3.11. Reduction in temperature increased solubility in both water and oil. As a rela-

TABLE 1. Partition Coefficients of Fluroxene at 37° C.

Phases	Number of Determinations	Partition Coefficient ± One S.D. or Range
Water/gas	10	0.84 ± 0.04
Blood/gas	8	1.37 ± 0.06
Oil/gas	8	47.7 ± 1.01
Grey matter/gas	4	1.96 ± 0.09
White matter/gas	3	1.96 (1.78-2.13)
Liver/gas	11	1.88 ± 0.29
Muscle/gas	14	3.11 ± 1.08

tively insoluble agent, it was predicted that onset and recovery from anesthesia with fluroxene would be rapid, intermediate between cyclopropane and halothane. Fluroxene can be predicted to provide a minimum alveolar anesthetic concentration of 3.5 per cent and to be slightly less potent than diethyl ether.

Fluroxene (Fluoromar) for this study was supplied by the Ohio Chemical & Surgical Equipment Co., Madison, Wisconsin.

References

1. Krantz, J. C., Jr., Carr, C. J., Lu, G., and Bell, F. K.: Anesthetic action of trifluoroethyl vinyl ether, *J. Pharmacol. Exp. Ther.* **108**: 488, 1953.
2. Sadove, M. S., Balagot, R. C., and Linde, H. W.: Trifluoroethylvinyl ether (Fluoromar); preliminary clinical and laboratory studies, *ANESTHESIOLOGY* **17**: 591, 1956.
3. Dundee, J. W., Linde, H. W., and Dripps, R. D.: Observations on trifluoroethylvinyl ether, *ANESTHESIOLOGY* **18**: 66, 1957.
4. Dornette, W. H. L., Miller, G. L., Sheffield, W. E., Cavallaro, R. J., and Poe, M. F.: Clinical experiences with trifluoroethylvinyl ether anesthesia, *Anesth. Analg.* **41**: 605, 1962.
5. Miller, G. L., and Dornette, W. H. L.: Flammability studies of Fluoromar-oxygen mixtures used in anesthesia, *Anesth. Analg.* **40**: 232, 1961.
6. Gramling, Z. W., and Volpitto, P. P.: Flammability of Fluoromar in the circle absorption system, *ANESTHESIOLOGY* **24**: 194, 1963.
7. Larson, C. P., Jr., Eger, E. I., II, and Severinghaus, J. W.: Solubility of halothane in blood and tissue homogenates, *ANESTHESIOLOGY* **23**: 349, 1962.
8. Lowe, H. J.: Personal communication.
9. Meyer, K. H., and Gottlieb-Billroth, H.: Theorie der narkose durch inhalationsanesthetika, *Hoppe-Seyler's Z. Physiol. Chem.* **112**: 55, 1920.
10. Meyer, K. H., and Hopff, H.: Theorie der narkose durch inhalationsanesthetika, *Hoppe-Seyler's Z. Physiol. Chem.* **126**: 281, 1923.
11. Eger, E. I., II, Shargel, R., and Merkel, G.: Solubility of diethyl ether in water, blood, and oil, *ANESTHESIOLOGY* **24**: 676, 1963.
12. Blumberg, A. G., La Du, B. N., Jr., Lesser, G. T., and Steele, J. M.: Determination of solubility of cyclopropane in fats and oils with use of Warburg apparatus, *J. Pharmacol. Exp. Ther.* **104**: 325, 1952.
13. Saidman, L. J., and Eger, E. I., II: Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia, *ANESTHESIOLOGY* **25**: 302, 1964.

COCAINE AND PSEUDOCOCAINE Stereoisomers of cocaine fail to exhibit the specific central stimulating effects of cocaine though the anesthetic effects at sensory nerve endings are practically the same. Likewise, pseudococaine does not produce euphoria as does cocaine, nor does it sensitize intact animals or isolated organs to catecholamines. Central action of cocaine and the phenomenon of potentiation of epinephrine seem to be related. Both amphetamine and cocaine produce a release of catecholamines in the central nervous system, particularly in the brainstem and reticular activating system. Electroencephalographic studies on rabbits and cats reveal that cocaine caused an arousal reaction while pseudococaine failed to show a similar effect. Effect of cocaine on the EEG was maintained when the brainstem was sectioned at the level of midpons but was abolished when the section was placed between pons and mesencephalon. Small doses of chlorpromazine completely abolished the activation caused by cocaine. Stimulating effect of cocaine on the brainstem could be explained by a change in sensitivity of the nervous tissue towards catecholamines in the brain. (*Lux, H. D., and Schmidt, G.: Electroencephalographic Investigations on the Effects of Cocaine and Pseudococaine, Naunyn-Schmiedeberg Arch. Exp. Pathol.* **246**: 452, 1964.)