Solubility of Diethyl Ether in Water, Blood and Oil

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MERKEL and Eger recently found that a minimal alveolar diethyl ether concentration of 3 to 3.5 per cent was required for anesthesia in dogs.[1] In this experiment, anesthesia was induced with cyclopropane. Following endotracheal intubation, cyclopropane was discontinued and ether added in flows sufficient (4–5 liters per minute) to eliminate cyclopropane concomitantly. An extension tube (30 ml.) was interposed between endotracheal tube and the anesthetic circuit to minimize contamination of end-tidal samples. End-tidal samples were intermittently drawn through an infrared analyzer from the proximal (animal) end of the extension tube. This analyzer was calibrated as described in "Methods." It was found that 3.28 per cent (range 3.0–3.5 in four dogs) alveolar ether was required to prevent gross movement in response to a clamp applied to the tail or in response to electrical currents applied to sensitive mucous membranes. It exceeds the concentration required to prevent response to a skin incision. This was taken as the minimum alveolar concentration of ether required for anesthesia.

When the commonly accepted blood/gas partition coefficients of 14.9[2] to 15.2[3] are used to convert this to milligrams per cent in blood, the resulting figures are 131 to 153 mg. per cent. These are considerably in excess of 80 to 120 mg. per cent[4,5] reported previously for the same state of anesthesia. Although no other agents (other than the cyclopropane) were used either as premedication or for induction or supplementation, 131 to 153 mg. per cent appeared to be too large to be credible. Both these figures and our technique were therefore subject to doubt. A third alternative was that the blood/gas partition coefficient was less than reported. In support of this, known values of saturated vapor density of ether and of weight of ether per 100 ml. of saturated solution may be used to predict a lower partition coefficient. Solubility of ether in 100 ml. of water-ether or saline-ether solution is 4.5 to 4.6 g. at 37° C. as determined by extrapolation from reported data.[6,7] We have repeated this determination using essentially the same technique as Hill[6] and obtained figures of 4.40 to 4.43 g./100 ml. water-ether solution at 37° C. Density of ether vapor at 37° C. is given as .34 to .35 g./100 ml.[8,9] If this is in the presence of a water solution 37° C., then the density will be reduced by the fraction occupied by water vapor. This fraction is equivilant to the rate of saturated vapor pressures of water and ether at 37° or $47/820 = .057$. Density of ether vapor in equilibrium with a saturated water solution may be calculated from the above at .32 to .33 g./100 ml. From these figures minimum and maximum partition coefficients at saturation at 37° C. may be calculated as $4.4/.33 = 13.3$ and $4.6/.32 = 14.4$, respectively. These are considerably less than 15.6[2] or 15.8[3] reported previously.

To further evaluate the possibility of error in prior reports the following work was done.

Method

With minor modifications the technique of Larson *et al.*[10] was used to determine partition coefficients. All determinations were made with the Beckman infrared halothane analyzer which is also sensitive to ether. The infrared head was filled with 100 per cent carbon dioxide plus a few drops of water to eliminate the cross-over effect of these substances. Calibration of the analyzer accompanied each series of determinations. Various aliquots of ether were injected into flasks of known volume. The resulting concentrations were calculated from the gas laws and the

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analyzer calibrated against these concentrations. All gases measured were saturated with water vapor (including the calibrating gases), and all measurements were made at 37° C. and 750 mm. of mercury pressure.

Results

The results found with Larson's technique are presented in table 1. As anticipated, the water/gas and blood/gas partition coefficients are somewhat lower than previously reported, being 13.09 and 12.14 respectively at concentrations used clinically. These values are significantly different from each other ($P < .01$). On the other hand, the oil/gas figure of 64.8 is considerably higher than 50 as reported by others.[11, 12] At higher equilibrium concentrations, it was found that the water/gas partition coefficient rose a small but statistically significant amount (table 1, experiments 1 to 4).

Discussion

The ether blood/gas partition coefficient of 12.13 is less than that found by others. The reason for the discrepancy is not known. Previous determinations have been chemical where ours has been physical. Our technique has proven quite accurate in the determination of halothane,[10] and has been confirmed by chemical analysis in the case of that agent.[13] This does not prove that the same accuracy exists in the case of ether. The low value obtained for ether could have resulted from inadequate equilibration but further incubation and agitation produced no change in solubility. Impurities in the ether according to the manufacturer are water and ethyl alcohol and amount to less than 2.5 per cent. The effect of these on the analyzer is essentially nil, and their dilutional effect has been accounted for in the calculations of solubility (actually no account of dilution need have been made since the same ether was used for calibration and experiment). Organic impurities, such as ethyl alcohol, might explain some of the older results obtained chemically. Ethyl alcohol would not be distinguished from ether with the techniques used; and since alcohol is highly water soluble, it would raise the apparent ether partition coefficient. Assuming the accuracy of the 12.13 figure allows a better correlation between the minimal alveolar ether concentration we have found necessary for anesthesia and blood concentrations of ether at the same anesthetic level reported by others. At 3 to 3.5 per cent alveolar concentration, a partition coefficient of 12.09 gives (assuming equilibrium between alveoli and arterial blood) an arterial concentration of 105 to 123 mg. per cent.

Our relative figures for blood and water are in agreement with those of others in that the partition coefficient for water is larger than that for blood. Shaffer and Rouzoni [2] gave a blood figure of 14.9 and a water figure of 15.8, while Haggard [3] gave similar figures of 15.2 and 15.6 for the respective solutes. In this regard, ether is unique among all known anesthetics.[14] The finding that the water/gas partition coefficient rises as the equilibrium concentration rises is similar to that reported for nitrous oxide in ox blood.[15] A similar but much greater effect has been shown by Nunn for oil/gas partition coefficients.[16] Although

TABLE 1. Ether Partition Coefficients at 37° C.

Experiment Number	Phases	Equilibrium Ether Concentration %	Range	Number of Determinations	Partition Coefficient ± One Standard Deviation	P Value for Comparison with Experiment I
1	water/gas	4.1	(1.7– 7.4)	9	13.09 ± .59	—
2	water/gas	13.2	(10.8–18.5)	7	13.56 ± 1.04	No significant difference
3	water/gas	39.6	(31.2–48.0)	7	13.98 ± .30	$P < .01$
4	water/gas	56.0	(52.0–69.0)	5	14.20 ± .20	$P < .001$
5	blood/gas*	8.9	(3.7–14.4)	7	12.13 ± .21	$P < .01$
6	oil/gas**	6.9	(2.9–11.4)	12	64.8 ± 4.6	

* The mean hemoglobin value was 13.4 g.
† Olive oil.

the rise is of statistical significance, it is too small to be of practical consequence. In contrast to our water and blood findings, the solubility of ether in olive oil is higher than reported previously. The oil/blood coefficient resulting equals 5.3 and is in fair agreement with Chenoweth's finding of 4.8 to 6.5 for ether fat/blood ratios after 2½ hours of anesthesia in the dog.[17] Agreement is not as good as it appears since fat is not oil but contains an appreciable amount of water and protein, perhaps 30–40 per cent. This should make the fat/blood coefficient lower than that for oil/blood. The fact that ether equilibrium between fat and blood is unlikely at 2½ hours also should make for a lower apparent coefficient. Possibly the solubility of ether in human fat is greater than its solubility in olive oil. However, this does not appear to be true for other anesthetics.

Summary

We have determined the solubility of ether in water, blood, and oil at 37° C. The ether water/gas partition coefficient was found to be 13.09; the blood/gas coefficient 12.13, and the oil/gas coefficient 64.8. These results are significantly different from those found in previous reports and are low for water and blood, and higher for oil.

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