Technical Note

Solubility Coefficients of Teflurane in Various Biological Media

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TEFLURANE, 1,1,1,2-tetrafluro-2-bromoethane is a nonflammable gaseous anesthetic agent. Artusio and colleagues studied the drug's action in both man [1] and dog [2, 3] and found it to provide a rapid induction, rapid recovery, and of a potency perhaps greater than cyclopropane.

We have determined the solubility coefficients (λ) for teflurane in water, human blood, oil, and human muscle, liver, and brain in order to understand and predict the course of uptake and distribution.

Method

At room temperature, teflurane exists over a liquid phase as a gas at a little over one atmosphere pressure. The technique of Larson *et al.*[4] was modified to account for the injections of aliquots of teflurane in the gaseous state. Teflurane was analyzed with the Beckman infrared halothane analyzer. A calibration curve for the infrared analyzer was constructed by adding known aliquots of teflurane to the flasks, after two or three drops of H_2O had been added, and calculating the theoretical concentration of teflurane in the flask at 37° C. The water was added to the flasks to provide us with a calibration curve accounting for the pressure broadening effect of water vapor on teflurane. Five gases of different concentrations prepared in this way were then flushed through the analyzer head. The concentration at full scale was 12.43 per cent and zero was set by room air. A reference tank of teflurane was prepared by adding 100 per cent oxygen from an "H" cylinder to teflurane by transfilling. It was set to the same reading before each group of determinations and was the standard for the calibration curve.

Human blood, either in a heparinized or citrated form, was obtained from the blood bank after expiration. Human tissues were obtained at autopsy from patients having died within 12 hours of autopsy. Tissues were refrigerated at 4–10° C. until used.

Results

Table 1 gives the tissue/gas partition coefficients at the various media studied. From these the tissue/blood partition coefficients in table 2 were calculated.

Discussion

Of the commonly used anesthetic agents, only ethylene has a lower solubility in water than teflurane. The blood/gas coefficient of 0.60 is greater than the values for N_2O ethylene, and cyclopropane, while the oil/gas

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

Phases	No. of Determinations	Partition Coefficients
Water/gas	13	0.32 ± 0.03
Blood*/gas	7	0.60 ± 0.05
Oil/gas	8	29.0 ± 0.8
Muscle/gas	4	2.26 (2.12–2.37)
Gray matter/gas	3	1.08 (0.94–1.20)
White matter/gas	3	1.15 (1.05–1.23)
Liver/gas	4	1.02 (0.93–1.15)
H_2O/gas (27° C.)	4	0.41 (0.39–0.43)
Oil/gas (27° C.)	4	35.75 (33.7–37.2)

* Mean Hematocrit: 43.

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TABLE 2. Tissue/Blood Partition Coefficients for Telflurane

Phase	Partition Coefficient
Muscle/blood	3.8
Gray matter/blood	1.8
White matter/blood	1.9
Liver/blood	1.7

coefficient is intermediate between cyclopropane and ether.[5]

From the blood/gas partition coefficient of 0.60, one can predict a relatively rapid induction of and recovery from anesthesia with this agent. It would compare with the rapidity of induction of cyclopropane with its blood/gas partition coefficient of 0.415. The oil/gas partition coefficient of 29.0 would indicate that this agent is much more potent than cyclopropane with its coefficient of 11.2.

Tissue/blood values for teflurane range from 1.7 to 3.8. These values are greater than those for cyclopropane or N_2O suggesting an increased tissue washout time of the agent with a consequently longer recovery period. The time constant (T.C.) of tissue washout—that is, the time it takes to reach 63 per cent of total washout—can be calculated if the tissue/blood partition coefficient and blood flow through an area are known.

$$\text{T.C.} = \frac{\text{tissue/blood partition coefficient}}{\text{blood flow/unit volume}}$$

For example, the time constant of nitrous oxide washout for gray matter (assuming a blood flow of 0.8 ml./g./minute) is $1.06/0.8 = 1.3$ minutes while that of teflurane is $1.8/0.8 = 2.3$ minutes. There would be an even greater discrepancy between the two agents in muscle since the blood flow to muscle is slower and the partition coefficient of teflurane greater. To illustrate the magnitude of difference in washout of tissue with different partition coefficients, one can compare the muscle washouts of cyclopropane, teflurane, and halothane. Teflurane and halothane have muscle/blood partition coefficients of 3.8 and 3.5, respectively. Using a blood flow of 0.4 ml./g./minute, these agents have time constants of 95 minutes and 88 minutes for muscle washout. On the other hand, cyclopropane with its muscle/blood coefficients of 0.91 has a time constant of 23 minutes.

An interesting finding in this experiment was the increase in solubility of teflurane in oil with decreasing temperature. The statement has been made that the solubility of anesthetic agents in oil would not increase with decreasing temperature as it does for water.[10] However, a fall of 10° C. increased the solubility of teflurane in H_2O by 23 per cent while it increased the solubility of teflurane in oil by 28 per cent. It is unlikely that other anesthetic agents would act any differently in this respect.

From the oil/gas partition coefficient, one can estimate the potency of an anesthetic agent.[6, 7] That is, the higher the oil/gas partition coefficient, the lower the alveolar anesthetic tension required to produce a given anesthetic state. A convenient standard by which different anesthetics may be compared is the minimum alveolar anesthetic concentration (MAC-1) required to prevent movement in response to a painful stimulus.[8] Using the value of MAC-1 for cyclopropane as 18 per cent,[9] we can predict a MAC-1 of $18 \times 11.2/29.0$ or 7.0 per cent for teflurane (11.2 is the oil/gas solubility of cyclopropane and 29.0 is the oil/gas solubility of teflurane). Our predictions from the solubility coefficients seem to be substantiated by the clinical observation of Artusio in both dogs and man. With approximately 50 per cent inspired teflurane, induction was quite rapid (90 seconds in dogs and two to three minutes in human beings). In dogs at 10 per cent teflurane, calculated by flow meter readings, light surgical anesthesia was produced. This 10 per cent inflowing concentration would result in a lower alveolar concentration so that a predicted MAC-1 of 7.0 per cent is reasonable.

Summary

Solubility coefficients (λ) for teflurane were measured and found to be 0.32 for water, 0.60 for blood, and 29.0 for oil. Tissue/gas values were gray matter, 1.08; white matter, 1.15; liver, 1.02; and muscle, 2.26. Tissue/blood coefficients are muscle, 3.8; gray

matter, 1.8; white matter, 1.9; and liver, 1.7. Reduction in temperature was found to increase solubility in both water and oil. From these figures one may predict that teflurane, compared to cyclopropane, should be almost as rapid in induction, slightly slower in recovery, and more potent.

Teflurane for this study was donated by Abbott Laboratories.

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RESPIRATORY DISTRESS SYNDROME The possibility that cardiac failure may be an important contributory or additive factor has led to the sporadic use of digitalis in the treatment of respiratory distress syndrome in newborn infants. To assess the value of such medication a double-blind controlled study was conducted on 196 newborn infants, using digoxin and a placebo. No significant difference was found between those infants given digoxin and those on the placebo, as judged by their progress over a four-day period and by the mortality rate. While there may be individual cases in which the clinician judges that an infant would benefit from digitalization, routine use of digoxin for the prevention of the respiratory distress syndrome is not recommended. (*Martin, J. K.: Controlled Trial of Digoxin in the Prevention of the Respiratory Distress Syndrome, Canada. Med. Ass. J. 89: 995 (Nov. 9) 1963.*)

CESARIAN SECTION Cesarian section was performed 2,316 times over a 17-year period without a maternal mortality. This record was attributed to adequate consultation, availability of blood, anesthesia, closer observation of the patient and the greater incidence of section hysterectomies. Anesthesia consisted of spinal in 96 per cent of cases, even in the face of shock or impending shock. The advantages of spinal anesthesia were: quicker and easier operation by giving better relaxation; smoother postoperative course; and fewer pulmonary complications. (*Pillsbury, S. G.: Safety of Cesarian Sections, Amer. J. Obstet. Gynec. 86: 580 (July) 1963.*)