J Anesth (1996) 10:276–281

Journal of
Anesthesia

Solubility of volatile anesthetics in plasma substitutes, albumin, intravenous fat emulsions, perfluorochemical emulsion, and aqueous solutions

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Abstract: Using the gas chromatographic headspace sampling technique, we determined the solubility of volatile anesthetics (halothane, enflurane, isoflurane, and sevoflurane) in plasma substitutes, albumin solution, intravenous fat emulsions, perfluorochemical FC-43 emulsion, and aqueous solutions at 37°C. The order of magnitude of λ value (liquid/gas partition coefficients) was halothane > enflurane > isoflurane > sevoflurane in all the parenteral infusion fluids except the perfluorochemical emulsion (FC-43). The FC-43/gas partition coefficients of the volatile anesthetics were almost the same at 5.5. The partition coefficients were affected by the osmolarity of solutions, hydrophobicity, and the structure of solutes. Also, the blood/gas partition coefficients in intravenous fat emulsions and FC-43 were calculated. It is suggested that fluid therapy, especially with intravenous fat emulsions or FC-43, may influence the blood/gas partition coefficients of anesthetics, and affect the induction of anesthesia.

Key words: Partition coefficient, Volatile anesthetics, Intravenous fat emulsion, Perfluorochemical emulsion, Hydroxyethyl starch solution

Introduction

The solubility of volatile anesthetics decreases with increasing osmolarity in aqueous solutions [1–4]. Recently, it has been demonstrated that the lower blood solubility of volatile anesthetics is correlated with a lower serum concentration of albumin and triglycerides [5,6].

The increase in liquid/gas partition coefficients of volatile anesthetics during administration of Fluosol-DA has also been reported. It is suggested that at clinically useful concentrations of Fluosol-DA, a significant delay in induction of inhalation anesthesia occurs [7]. The solubility of volatile anesthetics is expected to be high in hydrophobic macromolecular solutions. Induction of inhalation anesthesia might therefore be expected to be prolonged in patients treated with large volumes of parenteral infusion fluids, provided this high solubility also holds true for the parenteral infusion fluid. However, much of the data has been obtained from studies with aqueous solutions and blood. Studies concerning the solubility of volatile anesthetics in commercially available parenteral infusion fluids are limited.

In this study, we measured the concentration of volatile anesthetics in both the gas and liquid phase of aqueous solutions, plasma substitutes, albumin solution, intravenous fat emulsions, and FC-43. The liquid/gas partition coefficients, which denote the anesthetic's solubility in liquid, were calculated.

Address correspondence to: J. C. Shim
Received for publication on September 1, 1995; accepted on June 17, 1996

Materials and methods

Gas chromatography has been used to determine the concentration of volatile anesthetics with a variety of techniques. We used a modification of the method designed by Butler et al. [8]. A rigid sampling technique was found necessary for precise results and to maintain reproducibility of the volume delivered to the sampling bottle.

Parenteral infusion fluids and volatile anesthetics

We measured the solubility of volatile anesthetics in the following commercially available parenteral fluids: lactated Ringer's solution (Lactec, Otsuka, Tokushima, Japan), acetated Ringer's solution with or without 5% dextrose (Veen-F and Veen-D, Nikkenkagaku, Tokyo, Japan), sodium chloride solution (0.9%, 2.7%, and

5.4%, laboratory-prepared), dextrose solution (dextrose 5%, 10%, and 50%, Otsuka), human serum albumin solution (5% and 25% Albumin α, Green Cross, Osaka, Japan), hydroxyethyl starch solution (Hespander, Kyolin Pharmaceutics, Tokyo, Japan), dextran solution (Dextran 40 or Rheomacrodex in saline, and Dextran 70 or Macrodex in saline, Green Cross), intravenous fat emulsion (Intralipos, Green Cross), and perfluorochemical FC-43 emulsion (Oxypherol-E.T., Green Cross). The volatile anesthetics halothane (Fluothane, Takeda, Tokyo, Japan), enflurane (Ethrane, Dinabot, Tokyo, Japan), isoflurane (Forane, Dinabot), and sevoflurane (Sevoflurane, Maruishi, Osaka, Japan) were purchased from the respective pharmaceutical companies.

Gas chromatography and headspace sampling technique

The concentration of anesthetics in the gas and liquid phase was measured by Shimadzu GC-14B gas chromatography (Shimadzu, Kyoto, Japan) with automatic gas-sampling equipment (Headspace Sampler HSS-2B, Shimadzu) using the headspace sampling technique. This technique is often employed to determine the concentration of chemicals in the gas phase equilibrated with liquid or solid samples sealed in the sampling bottle under a constant temperature.

To separate the volatile anesthetics, we used a 30 m fused silica open tubular capillary column (0.546 mm internal diameter) coated with silicon-based polymers (polysiloxanes), polyethylene glycol, and solid absorbents. The column temperature was maintained at 50°C. A flame ionization detector was supplied by hydrogen and air at a flow rate of 50 ml·min^{-1} and 500 ml·min^{-1}, respectively. The carrier gas used was helium, flowing at a rate of 5.1 ml·min^{-1}.

Gas chromatographic peaks of volatile anesthetics and solution

We coupled the anesthetics presenting concurrently in aqueous solution so as not to overlap with the gas chromatographic peaks, considering the retention time of volatile anesthetics.

We also measured the gas chromatographic spectra of the solutions used in this study, and no interference was seen between these solutions and volatile anesthetics, except dextran solution and enflurane (the gas chromatographic retention time for enflurane and dextran was 2.074 min and 2.089 min, respectively). To determine the concentration of enflurane in dextran solution, we subtracted the gas chromatographic spectrum of dextran solution from that of enflurane, and obtained the corrected spectrum of enflurane.

Preparation of samples

First, 4 ml of each solution was poured into two glass bottles (25 ml in internal volume). The bottles were sealed with a teflon-coated stopper and clamped with an aluminum cap to ensure an airtight seal. As discussed above, we coupled the anesthetics presenting concurrently in aqueous solution so as not to overlap with the gas chromatographic peaks. Therefore, two sets of volatile anesthetics (halothane/sevoflurane, and isoflurane/enflurane) were added separately to the bottles. The volume of each anesthetic added to the bottle was 5 μl.

The bottle was kept at 37°C, and shaken vigorously for 30 s at 30-min intervals. Using an 18-gauge needle fitted with a stopcock, the stopper was pierced and the stopcock was briefly opened at 1-h intervals to equilibrate internal pressure with atmospheric pressure. Because the anesthetics equilibrated between the gas phase and solution within 2 h [9], we measured the concentrations of anesthetics at the 2nd, 3rd, 4th, and 5th h of incubation. Each 0.5 ml of the gas and solution was obtained from the incubation bottle for each gas chromatographic measurement. After sampling, the stopcock of the incubation bottle was briefly opened to equilibrate internal pressure with atmospheric pressure. Because the concentration of anesthetics in the incubation bottle decreased with repeated sampling, the bottles were incubated for 1 h to establish a new equilibrium of anesthetics between the gas and liquid phase.

Measurement of anesthetic concentration

Each 0.5-ml sample of the gas phase and solution, obtained from the incubation bottle, was separately introduced into the airtight bottle described above. The gas sample was introduced into a bottle in which 0.5 ml of the respective solution had been contained to ensure equal water vapor pressure with that of the sampling bottle for the liquid phase.

For the complete extraction of volatile anesthetics from the liquid phase, the heating temperature of the sampling bottle was set to 65°C (above the boiling point of the volatile anesthetics) for 10 min. Then, 800 μl of the gas phase was injected into the gas chromatography device using automatic gas sampling equipment.

Partition coefficient of volatile anesthetics

The liquid/gas partition coefficient(λ) of the volatile anesthetics was calculated using the following equation: $\lambda = C_{liq}/C_{gas}$, where C_{gas} and C_{liq} are the equilibrated concentrations of volatile anesthetic in the gas phase and the liquid phase, respectively. We confirmed that

the peak area from gas chromatography was related linearly to the concentration of anesthetic over the entire range of concentrations studied.

We demonstrated an identical gas chromatographic peak area for both the gas and liquid phase of anesthetics in the preliminary study. The predetermined concentrations of anesthetics for both phases were equal. The results quoted above showed an accuracy and a precision acceptable for our gas chromatographic method.

Osmolarity

The osmolarity of solutions was calculated from the freezing point depression of solutions, using an Osmometer (Roebling, Berlin, Germany), which was calibrated to 308 mOsm/l using normal saline. Thus, we measured osmolarity at 0°C.

Statistics

Linear regression analysis was applied to the data of each anesthetic. Differences between the liquid/gas partition coefficients for the anesthetics were tested using the analysis of variance (ANOVA) and Scheffé's test. We considered $P < 0.05$ statistically significant. All values obtained were mean ± SD.

Results

The liquid/gas partition coefficients of each volatile anesthetic in this study are shown in Table 1. We have also listed the partition coefficients for distilled water reported previously [1,10]. Those are similar to the present results.

The order of magnitude of λ (liquid/gas partition coefficients) was halothane > enflurane > isoflurane > sevoflurane in all the parenteral infusion fluids except perfluorochemical emulsion (FC-43). The FC-43/gas partition coefficients of the anesthetics were almost the same at 5.5 (Table 1).

Discussion

Dextrose and NaCl solutions

With increasing concentrations of dextrose and NaCl solutions, osmolarity at 0°C increased and the partition coefficient decreased (Table 1). The partition coefficients of volatile anesthetics decreased linearly when osmolarity increased (Fig. 1). In aqueous solutions, these solutes are composed of relatively small molecules with no inherent anesthetic binding sites. Thus, the solubility of anesthetics in aqueous solutions was independent of the molecular structure of the solute and dependent only on osmolarity [1].

Table 1. Liquid/gas partition coefficients of volatile anesthetics in distilled water, aqueous solutions, plasma substitutes, intravenous fat emulsions, and perfluorochemical emulsion

Solution	Osmolarity (mOsm/l)	Halothane	Enflurane	Isoflurane	Sevoflurane
Distilled water	0	0.79 ± 0.04 (31) 0.859 [1][a]	0.74 ± 0.04 (25) 0.754 [1][a]	0.58 ± 0.03 (33) 0.626 [1][a]	0.37 ± 0.02 (32) 0.36 [10][a]
Dextrose 5%	309	0.78 ± 0.05 (8)	0.70 ± 0.02 (8)	0.55 ± 0.01 (8)	0.33 ± 0.01 (8)
Dextrose 10%	638	0.75 ± 0.03 (8)	0.63 ± 0.03 (8)	0.49 ± 0.02 (8)	0.29 ± 0.01 (8)
Dextrose 50%	3090	0.47 ± 0.02 (8)	0.33 ± 0.01 (8)	0.26 ± 0.01 (8)	0.12 ± 0.01 (8)
NaCl 0.9%	308	0.76 ± 0.02 (11)	0.66 ± 0.04 (12)	0.51 ± 0.03 (12)	0.32 ± 0.02 (11)
NaCl 2.7%	924	0.63 ± 0.02 (8)	0.56 ± 0.02 (8)	0.44 ± 0.01 (8)	0.27 ± 0.01 (8)
NaCl 5.4%	1848	0.51 ± 0.01 (6)	0.45 ± 0.02 (7)	0.35 ± 0.02 (8)	0.21 ± 0.01 (7)
Lactated Ringer's	267	0.75 ± 0.03 (6)	0.69 ± 0.03 (6)	0.54 ± 0.02[$] (7)	0.32 ± 0.01 (7)
Acetated Ringer's	268	0.72 ± 0.02[$] (7)	0.69 ± 0.03 (6)	0.56 ± 0.02[$] (7)	0.33 ± 0.02 (8)
Acetated Ringer's 5% dextrose	601	0.71 ± 0.03[#] (7)	0.64 ± 0.04 (7)	0.50 ± 0.03[#] (8)	0.29 ± 0.01[#] (7)
Hydroxyethyl starch solution	297	0.83 ± 0.03 (5)	0.74 ± 0.02 (6)	0.58 ± 0.02 (6)	0.35 ± 0.02 (6)
Dextran 40	309	0.73 ± 0.03* (9)	0.64 ± 0.03* (9)	0.49 ± 0.02* (12)	0.30 ± 0.02* (12)
Dextran 70	311	0.72 ± 0.03* (9)	0.64 ± 0.04* (11)	0.50 ± 0.02* (11)	0.30 ± 0.01* (10)
Plasma albumin 5%	274	1.67 ± 0.09 (14)	1.17 ± 0.06 (14)	0.97 ± 0.06 (14)	0.52 ± 0.02 (14)
Plasma albumin 25%	283	5.42 ± 0.54 (11)	3.23 ± 0.24 (14)	2.74 ± 0.23 (14)	1.31 ± 0.11 (11)
Intralipid 10%	287	23.91 ± 1.78 (7)	12.96 ± 0.44 (7)	11.38 ± 0.50 (8)	6.38 ± 0.42 (7)
Intralipid 20%	321	43.30 ± 4.74 (11)	22.40 ± 1.90 (11)	20.55 ± 1.42 (11)	10.95 ± 1.03 (7)
FC-43 emulsion	341	5.54 ± 0.34 (6)	5.78 ± 0.11 (7)	5.60 ± 0.18 (7)	5.35 ± 0.28 (6)

All values are means ± SD. Sample numbers are noted in parentheses.
[$], [#], and *, $P < 0.05$ *vs* 0.9% NaCl, 10% dextrose, and hydroxyethyl starch solution, respectively.
[a] Previously reported values [1,10] of water/gas partition coefficients are given for comparison.

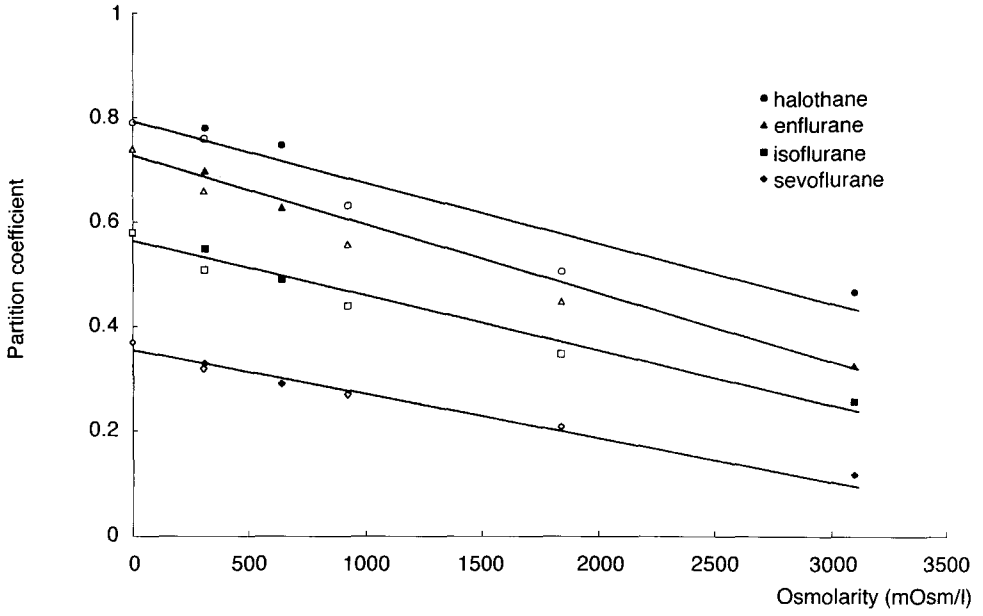

Fig. 1. Effect of osmolarity on partition coefficient of volatile anesthetics in NaCl and dextrose solutions. Lines are drawn by linear regression analysis. *Open symbols*, NaCl solution; *closed symbols*, dextrose solution. The linear regression parameters are as follows: halothane: $y = -1.167E - 4x + 0.789$; enflurane: $y = -1.320E - 4x + 0.716$; isoflurane: $y = -1.026E - 4x + 0.559$; and sevoflurane: $y = -0.764E - 4x + 0.350$

The linear regression parameters between the partition coefficients and osmolarity are shown in Fig. 1. The slope of isoflurane was in good agreement with the value reported by Lerman et al. [1], but those of halothane and enflurane were lower. The parameters for sevoflurane have never been reported before. Lerman et al. [1] measured the partition coefficients in NaCl, dextrose, mannitol, and heparin solutions, and their osmolarity range was higher than ours. This may explain the difference in linear regression parameters between this study and that of Lerman et al. [1].

The partition coefficients in 0.9% NaCl were lower than those in 5% dextrose solution, whereas the osmolarity of both solutions was identical. In this study, osmolarity was measured at 0°C, and the partition coefficient was determined at 37°C. Because NaCl solutions are dissociated more easily at high temperatures, the increase in osmolarity of NaCl solutions might be larger than those of dextrose solutions at 37°C. The effect of temperature on osmolarity might affect the results. However, no mention is made in Lerman's [1] article of the method used to determine osmolarity, and we cannot discuss this issue in further detail.

Ringer's solution

The partition coefficients in lactated or acetated Ringer's solution were lower than those in distilled water, and close to those in 0.9% NaCl solution (Table 1). The osmolarity of these solutions are almost equal to that of 0.9% NaCl solution. Thus, the reduction in partition coefficient might be due to the high osmolarity of Ringer's solution.

However, the partition coefficients of halothane in acetated Ringer's solution, and of isoflurane in lactated and acetated Ringer's solution, were significantly lower than in 0.9% NaCl solution. Furthermore, the partition coefficients of halothane, isoflurane, and sevoflurane in acetated Ringer's solution with 5% dextrose were significantly lower than those in 10% dextrose solution, whereas the osmolarity of these solutions were almost identical (Table 1). The effects of buffer and other ions were not examined in this study, and further investigation is necessary.

Hydroxyethyl starch and dextran

Both hydroxyethyl starch and dextran are high-molecular-weight compounds and are used as plasma expanders in clinical practice. Even though the osmolarity of these solutions are similar, the partition coefficients of anesthetics in hydroxyethyl starch solution are significantly higher than those in dextran solution (Table 1). Hydroxyethyl starch is a derivative of amylopectin, a waxy starch containing branched chains of glycoside molecules, whereas dextran has a linear polymer structure [11]. The difference in the molecular structure between hydroxyethyl starch and dextran may affect the partition coefficients of anesthetics.

Intravenous fat emulsions and albumin

Intravenous fat emulsions and albumin are hydrophobic molecules, and the partition coefficients in these solutions were higher than those in distilled water. Furthermore, the partition coefficients in intravenous fat

emulsion 20% were about 20–40 times higher than those in the other solutions.

The partition coefficient in intravenous fat emulsion 20% was approximately two times greater than that in intravenous fat emulsion 10% for all four volatile anesthetics. Also, the partition coefficient in 25% albumin solution is three times the partition coefficient in 5% albumin solution (Table 1). This reflects the likelihood that the λ value of volatile anesthetics in intralipids is concentration-dependent. This relationship indicates that anesthetic molecules bind to hydrophobic molecules, and the partition coefficients in these solutions thus increase.

Perfluorochemical emulsion

The partition coefficients of halothane, enflurane, isoflurane, and sevoflurane for most of the parenteral infusion fluids, except FC-43, decreased in that order. Also, the order in liquid/gas partition coefficients among the four anesthetics during administration of Fluosol-DA did not parallel the order seen with other parenteral infusion fluids [7].

The interaction between volatile anesthetics and perfluorochemicals is not same as that between these anesthetics and hydrocarbon derivatives such as lipids, sugar, and protein, which are the solutes of parenteral infusion fluids. The possible explanation for the discrepancy in the order of solubility between FC-43 and the other parenteral infusion fluids can be given as follows: First, in contrast to aqueous solutions, it is possible that the solubility of anesthetics in perfluorocarbon (PFC) depends on the molecular structure of the solute. Second, the relative solubility of volatile anesthetics depends on the size of their dipole moment and molecule [1]. The difference in relative solubility which is determined by the interaction between FC-43 and anesthetics may also account for the discrepancy in the orders of λ values. Third, in contrast to parenteral infusion fluids, gas transport by FC-43 is based on the enhanced solubility caused by the physics of the molecules involved, making them less polar [12]. The change of polarity of volatile anesthetics may thus influence their solubility.

In the present study, the differences between the λ values among volatile anesthetics in FC-43 were not significant. Chilcoat et al. [7] and Tremper et al. [13] also reported that the λ values were around 7. That the values are roughly similar in our study is consistent with the findings of Chilcoat et al. [7].

Effect of fluid therapy on induction of anesthesia

An increase in osmolarity decreased the solubility of volatile anesthetics linearly (Fig. 1). The induction of anesthesia may be quickened by a decrease in solubility. However, it is suggested that the rate of decrease in solubility caused by increasing osmolarity in circulating blood is too small to affect the induction of anesthesia.

The increase in blood/gas partition coefficients is related to the prolongation of induction of anesthesia. In the present study, we demonstrated the increased value of the partition coefficients of volatile anesthetics in intravenous fat emulsions, albumin solution, and FC-43. It is suggested that both the composition of blood and the partition coefficients of the anesthetics may be changed by fluid therapy with a large volume of these parenteral infusion fluids, and that the induction of anesthesia may thus be affected.

We estimated the blood/gas partition coefficient of volatile anesthetics assuming the presence of

Table 2. Estimation of partition coefficients of volatile anesthetics during infusion of intravenous fat emulsion and FC-43

	Percentage of solution in blood	Halothane	Enflurane	Isoflurane	Sevoflurane
Blood		2.30 (1.00)	1.78 (1.00)	1.41 (1.00)	0.69 (1.00)
Intravenous fat emulsion 20%	1	2.71 (1.18)	1.99 (1.12)	1.60 (1.13)	0.79 (1.15)
	5	4.35 (1.29)	2.81 (1.580)	2.37 (1.68)	1.20 (1.75)
	100	43.3 (18.8)	22.4 (12.6)	20.6 (14.6)	11.0 (16.0)
FC-43	20	2.95 (1.28)	2.58 (1.45)	2.25 (1.60)	1.62 (2.36)
	40	3.60 (1.57)	3.38 (1.90)	3.09 (2.19)	2.55 (3.72)
	100	5.54 (2.41)	5.78 (3.25)	5.60 (3.97)	5.35 (7.80)

The values were calculated from the following equation: $\lambda_E = \lambda_B \cdot (1 - \alpha) + \lambda_x \cdot \alpha$, where λ_E, λ_B, and λ_x are the estimated partition coefficient, partition coefficient in blood, and partition coefficient in x (intravenous fat emulsion or FC-43), respectively. α is the fraction of solution in blood. The values in parentheses are values of solubility converted to an equivalent blood/gas partition coefficient of halothane, enflurane, isoflurane, and sevoflurane, respectively.

intravenous fat emulsion and FC-43 in circulating blood (Table 2). The values in parentheses are the value of solubility converted to an equivalent blood/gas partition coefficient of halothane, enflurane, isoflurane, and sevoflurane, respectively (Table 2).

When an intravenous fat emulsion constitutes 1% or 5% of the total circulating blood volume, respectively, the blood/gas partition coefficient is estimated to be 1.12 to 1.75 times higher than that without intravenous fat emulsion in the circulation (Table 2). As blood/gas partition coefficients depend to some extent on the concentration of several serum lipid and protein constituents [5,6], we attributed this increase in solubility to the constituents of intravenous fat emulsion: phospholipid liposomes and triglyceride emulsion particles.

However, as far as the increased solubility of volatile anesthetics in intravenous fat emulsion is concerned, it is uncertain whether intravenous fat emulsion being metabolized and diluted in circulating blood reflects this effect on delaying the induction of anesthesia. However, the changes in measured serum lipid components with infusion of an intravenous fat emulsion are well documented [14,15]. Infusion of intravenous fat emulsion 20% increased plasma concentrations of triglycerides, free fatty acids, and lipoprotein lipase. When triglycerides were continuously infused at a rate of $0.17\,g \cdot kg^{-1} \cdot h^{-1}$ for 6 h, the plasma concentration reached a plateau during the 3rd to 5th h of continuous infusion [14]. Serum concentrations of triglycerides and free fatty acids increased significantly during infusion of intravenous fat emulsion 10%. Serum triglycerides increased to 126 and 138 mg/dl at 30 and 60 min after the start of the emulsion infusion, respectively, and the change in these concentrations lasted 2 h after the termination of infusion [15]. The validity of this effect on solubility could be established if we measured directly the alveolar/inspired volatile anesthetic ratio. Further research is needed to reach conclusive results.

The partition coefficients in FC-43 are 2.41 to 7.80 times greater than the blood/gas partition coefficients, and are not as large as those in intravenous fat emulsion. The purpose of PFC infusion is to maintain the oxygen-carrying capacity of circulating blood. However, the clinically useful plasma concentration of Fluosol-DA, typically 20%–25%, is much higher than that of intravenous fat emulsion [7]. We calculated the blood/gas partition coefficients assuming that the FC-43 plasma concentration is 20% and 40%, respectively (Table 2). The increase in partition coefficients is drastic and it is suggested that the infusion of FC-43 may prolong the induction of anesthesia. We should note that the increments in blood/gas partition coefficient of each anesthetic were different, because the partition coefficients of each volatile anesthetic in FC-43 were almost the same at 5.5. For sevoflurane, the blood/gas partition coefficient with 40% FC-43 is 3.72 times larger than that without FC-43, where as it is only 1.57 times larger for halothane.

We have not examined the effects of FC-43 on blood/gas partition coefficients in vivo. Further investigation of this issue is necessary.

Acknowledgments. This study was supported in part by a Grant-in-Aid for General Scientific Research (B) 07457363 from the Ministry of Education, Science, and Culture of Japan. The authors wish to thank Ms. Chika Okumura for her technical assistance.

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