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The Blood/Gas Solubilities of Sevoflurane, Isoflurane, Halothane, and Serum Constituent Concentrations in Neonates and Adults

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To determine the effect of prematurity on the solubility of volatile anesthetics in blood, the authors measured the blood/gas partition coefficients of sevoflurane, isoflurane, and halothane and the serum concentrations of albumin, globulin, cholesterol, and triglycerides in umbilical venous blood from ten preterm and eight full-term neonates and in venous blood from eight fasting adult volunteers. The authors found that the blood/gas partition coefficient of sevoflurane did not differ significantly among the three age groups. The partition coefficients of isoflurane and halothane in preterm neonates did not differ significantly from those in full-term neonates. However, the partition coefficients of both anesthetics in neonates were significantly less than those in adults. The blood/gas partition coefficients of the three volatile anesthetics in preterm neonates did not change significantly with gestational age. The blood/gas partition coefficients of sevoflurane, isoflurane and halothane for all three age groups combined correlated only with the serum concentration of cholesterol. The authors conclude that the blood/gas partition coefficients of isoflurane, halothane, and sevoflurane in preterm neonates are similar to those in full term neonates and that gestational age does not significantly affect the blood/gas solubility. (Key words: Age factors: adult; full-term; neonate; preterm. Anesthesia: adult; neonatal; pediatric. Anesthetics, volatile: halothane; isoflurane; sevoflurane. Blood: albumin; cholesterol; globulin; triglycerides. Solubility: blood; partition coefficient.)

THE MORE RAPID rate of rise of the alveolar to inspired anesthetic partial pressures in full-term neonates and children compared with adults may be explained in part by the lower blood solubility of volatile anesthetics in neonates and children.[1–3] This lower solubility has been attributed to lower serum concentrations of proteins and lipids in neonates and children than in adults.[1] Although the rate of rise of alveolar to inspired anesthetic partial pressures in preterm neonates has not been established, clinical experience suggests that induction of anesthesia with volatile anesthetics is very rapid in these infants. We hypothesized that the apparent rapid rise of alveolar to inspired anesthetic partial pressure in preterm neonates may be explained by lower blood/gas partition coefficients of volatile anesthetics in these infants compared with older children. Evidence to support this hypothesis is based on the lower concentrations of serum constituents in preterm neonates compared with older children.[4,5] To explore this hypothesis, we measured the blood/gas partition coefficients of sevoflurane, isoflurane, and halothane in preterm and full-term neonates at delivery and in adult volunteers and correlated these coefficients with the serum concentrations of albumin, globulin, cholesterol, and trigylcerides.

Methods

After institutional approval was obtained, three groups of subjects were investigated—preterm neonates, full-term neonates, and healthy fasting adult volunteers. Fifteen milliliters of blood were collected from the umbilical vein of the placenta immediately after delivery of the neonates and from a peripheral vein of the adults. Each blood sample was divided into two aliquots: a 12-ml aliquot was used to measure the blood/gas partition coefficients in triplicate of sevoflurane, isoflurane, and halothane as described previously[6,7] and a 3-ml aliquot was used to analyze of the serum concentrations of albumin, globulin, cholesterol, and triglycerides.

The blood/gas partition coefficients were measured in triplicate as follows: 4 ml of blood were added to a 20-ml glass syringe fitted with a nylon stopcock. The plunger of the syringe was coated with silicone grease to ensure an airtight seal. Sixteen milliliters of a gaseous mixture of 0.5% sevoflurane, 1% isoflurane, and 1% halothane in air were then aspirated into the syringe. The syringe was shaken vigorously for 30 s and immersed in a thermostatically controlled water bath, heated to 37° C, for 2 h to allow equilibration of anesthetic between the gas and blood phases. The syringe was shaken vigorously every 15 min during the 2-h equilibration period. At the completion of the 2-h period, the concentrations of volatile anesthetics in the gas phase were measured by gas chromatography. After expelling all of the gas phase from the syringe, a 2-ml aliquot of blood was then transferred anaerobically into an evacuated 280-ml flask. The vacuum in the flask was gradually dissipated by opening the stopcock to the atmosphere while the contents of the flask were equilibrating in the 37° C water bath. The flask was shaken vigorously every 15 min over a 2-h period to ensure equilibration of anesthetic between the blood and gas phases. At the end of 2 h the concentrations of volatile anesthetics in the gas phase of the flask were measured by gas chromatography.

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The gas chromatograph used in this study consisted of a column containing 10% SF-96 on chromosorb WHP 60/80 mesh, 0.32 cm × 360 cm, and a flame ionization detector supplied with an air/hydrogen gas mixture (flow rates of 280 and 40 ml/min, respectively). The carrier gas used was nitrogen, flowing at a rate of 40 ml/min.

The blood/gas partition coefficients (λ) of the volatile anesthetics were calculated using the following equation[7]:

$$\lambda = \frac{C_s \cdot (V_f/V_s)}{C_s - C_f}$$

where C_s is the concentration of volatile anesthetic in the gas phase of the 20-ml syringe, C_f is the concentration of volatile anesthetic in the gas phase of the 280-ml flask, V_f is the volume of the flask, and V_s is the volume of the aliquot of blood transferred to the flask.

Parametric data were compared using one-way ANOVA with the corrected Tukey HSD test for multiple pairwise comparisons.[8,9] The relationships between the blood/gas partition coefficients of the four anesthetics and gestational age were determined using the least squares linear regression analysis. The slopes of the relationships between the blood/gas partition coefficients and gestational age were tested using Student's t test.[9] Power analysis was performed to determine the likelihood of finding a significant relationship between the partition coefficients and gestational age ($\alpha_2 = 0.05$).[9] The correlation of blood/gas partition coefficients with the concentrations of serum constituents were analyzed using stepwise regression analysis. Statistical significance ($P < 0.05$) was accepted.

Results

We studied ten preterm neonates, eight full-term neonates, and eight adults. In each age group the blood/gas partition coefficients followed the order: sevoflurane < isoflurane < halothane (table 1). The blood/gas partition coefficient of sevoflurane did not differ significantly among the three age groups studied. Although the partition coefficients of isoflurane and halothane in preterm neonates did not differ significantly from those in full-term neonates, the partition coefficients for both anesthetics in the two groups of neonates were significantly less than those in adults ($P < 0.05$; table 1).

For preterm neonates there was no relationship between gestational age and the blood/gas partition coefficients (slopes: $P > 0.05$; r^2: sevoflurane 0.314, isoflurane 0.096, and halothane 0.053). By power analysis, we determined that the 95% likehood of detecting a slope that differed significantly from zero was 62% for sevoflurane, 87% for isoflurane, and 91% for halothane.

Mean serum concentrations of albumin in both groups of neonates were significantly less than those in adults. The mean serum concentrations of cholesterol were significantly different among the three age groups: full-term neonates < preterm neonates < adults ($P < 0.05$). There were no significant differences in the serum concentrations of globulin or triglyceride among the three age groups.

Stepwise linear regression analysis demonstrated a significant relationship between the blood/gas partition coefficients of the three anesthetic agents and the serum concentration of cholesterol (table 2). However, the serum concentrations of albumin, globulin, and triglyceride did not contribute significantly to the prediction of the partition coefficients of any of the anesthetic agents.

Discussion

The blood/gas partition coefficients of isoflurane and halothane in full-term neonates and adults are consistent with those published previously.[1,10] The lower blood/gas partition coefficients of isoflurane and halothane in preterm and full-term neonates compared with adults con-

TABLE 1. Blood/Gas Partition Coefficients and Concentrations of Serum Constituents

Age Groups	No.	Age	Partition Coefficients			Serum Constituents			
			Sevoflurane	Isoflurane	Halothane	Albumin (gm/l)	Globulin (gm/l)	Cholesterol (mM)	Triglycerides (mM)
Preterm neonates	10	31.6 ± 2.8 wks	0.66 ± 0.019	1.23* ± 0.142	2.26* ± 0.142	32.2‡ ± 6.96	22.32 ± 8.87	2.48‡ ± 0.68	0.91 ± 1.05
Full-term neonates	8	39 ± 0.8 wks	0.66 ± 0.036	1.25† ± 0.069	2.26* ± 0.137	27.5§ ± 7.43	17.75 ± 6.16	1.66* ± 0.35	0.47 ± 0.29
Adults	8	35 ± 4.8 yrs	0.68 ± 0.019	1.38 ± 0.057	2.57 ± 0.146	41.38 ± 4.47	25.63 ± 4.03	4.11 ± 0.62	1.04 ± 0.18

Data are mean ± SD.
* $P < 0.001$ compared with adults.
† $P < 0.005$ compared with adults.
‡ $P < 0.05$ compared with adults.
§ $P < 0.01$ compared with adults.

TABLE 2. Stepwise Regression Analysis of the Blood/Gas Partition Coefficients on the Serum Constituents

Anesthetic Agents	Albumin		Globulin		Cholesterol		Triglyceride	
	r^2	F Test	r^2	F Test	r^2	F Test	r^2	F Test
Sevoflurane	0.07	1.838^2	0.004	0.111^4	0.18	5.155^1	0.05	0.784^3
Isoflurane	0.005	0.271^4	0.023	0.761^2	0.35	14.704^1	0.15	0.739^3
Halothane	0.016	0.276^2	0.002	0.071^3	0.45	19.67^1	0.017	0.062^4

The stepwise linear regression analysis was performed on the pooled data of the 26 subjects. Superscripts denote the priority assigned to the serum constituents in the regression model (1 = high priority; 4 = low priority). Only cholesterol levels correlated significantly (F-to-enter = 4.26, $\alpha = 0.05$) with the blood/gas partition coefficient data.

tribute in part to the more rapid rate of rise of the alveolar to inspired anesthetic partial pressures reported previously and, thus, to a more rapid induction of anesthesia in neonates.[2,3] Although it is our clinical impression that induction of anesthesia with halothane or isoflurane is more rapid in preterm neonates than it is in full-term neonates, this impression cannot be attributed to lower blood/gas partition coefficients in preterm neonates.

Our estimate of the partition coefficient for sevoflurane in adults is consistent with previously published data.[7] We found no significant effect of age on the blood/gas partition coefficient of sevoflurane in the two groups of neonates compared with adults. This is consistent with the findings of Strum *et al.* who noted no age related effect on the partition coefficient of sevoflurane in young adults and elderly adults.[7] The absence of an age effect may be due to the low blood/gas solubility of sevoflurane and the high signal-to-noise ratio as the solubility approaches zero.[7]

Several investigators have attempted to identify those factors that determine the solubility of volatile anesthetics in blood. Saraiva *et al.* found that only the serum concentration of triglyceride predicted the blood/gas partition coefficient of halothane.[11] This was not supported by the work of Pang *et al.* and Laasberg *et al.* who suggested that albumin was the serum constituent that determined the partition coefficient of halothane in blood.[12,13] Recently Lerman *et al.* demonstrated a significant correlation between the blood/gas partition coefficient of isoflurane and enflurane and the serum concentrations of albumin and triglyceride and between the partition coefficient of halothane and methoxyflurane and the serum concentrations of albumin, globulin, cholesterol, and triglyceride.[1] In the present study, we demonstrated that the serum concentration of cholesterol predicted 18% of the blood solubility in the case of sevoflurane, 35% in the case of isoflurane, and 45% in the case of halothane. The serum concentrations of the other three constituents, however, did not predict singularly or in combination the blood/gas partition coefficients of the three volatile anesthetics. The differences among the results of these studies may be attributed to the narrow ranges and large scatter of serum concentrations of constituents in the age groups studied and to differences in the sampling and laboratory techniques at each institution. Although it is possible that serum constituents other than those investigated in this study may be responsible for the solubility of volatile anesthetics in blood, few have been studied. The effects of α_1 acid glycoprotein on the solubility of volatile anesthetics in blood were investigated recently and were shown not to affect the blood solubility of halothane, enflurane, and sevoflurane.[14] The effects of other serum constituents on the blood/gas solubility of volatile anesthetics in blood are currently under investigation. At present, the evidence correlating the blood/gas partition coefficients of volatile anesthetics with the serum constituents remains to be clarified.

In summary, we found no statistically significant differences in the blood/gas partition coefficients of sevoflurane, isoflurane, and halothane between preterm and full-term neonates, nor did we find a correlation between gestational age and the blood/gas partition coefficients of the three anesthetics in preterm neonates. Although the blood/gas partition coefficient of sevoflurane in neonates did not differ significantly from that in adults, the coefficients of isoflurane and halothane were significantly less in both groups of neonates than they were in adults.

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