Anesthesiology
61:139-143, 1984

Age and Solubility of Volatile Anesthetics in Blood

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The more rapid rate of rise of alveolar anesthetic partial pressure in children compared with adults may be explained in part by an increasing solubility of volatile anesthetics in blood with age. To investigate this possibility, the authors measured the blood–gas partition coefficients of isoflurane, enflurane, halothane, and methoxyflurane in four groups of fasting subjects: 10 full-term newborns (at delivery), 11 children (3–7 years old), 11 adults (20–40 years old), and 10 elderly adults (75–85 years old). The blood–gas partition coefficients were greatest in adults: isoflurane 1.46, enflurane 2.07, halothane 2.65, and methoxyflurane 16.0; and least in newborns: 1.19, 1.78, 2.14, 13.3, respectively. The blood–gas partition coefficients in children (1.28, 1.78, 2.39, 15.0, respectively), which were intermediate between those in newborns ($P < 0.005$) and those in adults ($P < 0.005$), were not significantly different from those in elderly adults (1.29, 1.79, 2.41, 15.0, respectively). The blood–gas partition coefficients of both isoflurane and enflurane correlated directly with the serum albumin and triglyceride concentrations; that of halothane correlated directly with the serum cholesterol, albumin, triglyceride, and globulin concentrations; and that of methoxyflurane correlated directly with the serum cholesterol, albumin, and globulin concentrations. The authors conclude that 1) age significantly affects blood–gas partition coefficients, and 2) the lower blood–gas partition coefficients in children explain in part the more rapid rise of alveolar anesthetic partial pressure in this age group. (Key words: Age factors: anesthetic solubility. Anesthesia: geriatric; neonatal; pediatric. Anesthetics, volatile: enflurane; halothane; isoflurane; methoxyflurane. Solubility: blood; partition coefficient.)

THE RATE of induction of anesthesia is proportional to the rate of rise of alveolar toward inspired anesthetic partial pressures, and both are more rapid in infants[1,2] and children[2] than in adults. This more rapid rate of rise of alveolar anesthetic partial pressure¶ has been attributed to three factors: 1) a larger ratio of alveolar ventilation to functional residual capacity; 2) the delivery of a greater fraction of the cardiac output to vessel-rich organs; and 3) a greater cardiac output per kilogram body mass.[1] Results from a mathematic model that simulated the rate of rise of alveolar anesthetic partial pressure and that included these factors, qualitatively supported this difference between children and adults.[3] However, the rate of rise of alveolar anesthetic partial pressure in children based on the mathematic model was slower than the rate of rise of alveolar anesthetic partial pressure from the *in vivo* measurements. Because the blood–gas partition coefficients for children in the mathematic model were assumed to be the same as those for adults, the discrepancy between the results from the model and the *in vivo* measurements in children might be explained by an unrecognized difference in the blood–gas partition coefficients between children and adults.[1-4]

Furthermore, the concentrations of serum proteins and serum lipids are less in infants and children than in adults.[5-7] Because the blood–gas partition coefficient depends on the concentrations of these serum constituents,[8-12] this was further evidence suggesting that the blood–gas partition coefficients in infants and children may in fact be less than in adults.[2,3] Therefore, we studied the effect of age on the solubility of volatile anesthetics in blood by measuring the blood–gas partition coefficients of isoflurane, enflurane, halothane, and methoxyflurane *in vitro* in blood from newborns, children, adults, and elderly adults.

Methods

This study was approved by our Committee on Human Research, and verbal consent was obtained from each patient or parent where appropriate.

We studied four groups of fasting subjects (ASA 1 and 2): 10 full-term newborns (at delivery); 11 children (3–7 years old) at induction of anesthesia; 11 adult volunteers (20–40 years old); and 10 elderly adults (75–85 years old), three of whom were volunteers and seven of whom were patients at induction of anesthesia. We collected 15 ml blood from each of the newborns by placental venipuncture and from each of the remaining 32 subjects by venipuncture or retrograde flow through an intravenous or arterial catheter. Before collecting each aliquot of blood, we flushed the deadspace of the catheter thoroughly. We divided the blood from each subject into two specimens: a 7-ml specimen, anticoagulated with EDTA, for determination of the blood–gas partition coefficients

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¶ Defined as the fractional ratio of the alveolar to inspired anesthetic partial pressure.

Received from the Departments of Anesthesia and Pediatrics, and the Cardiovascular Research Institute, University of California, San Francisco, California. Accepted for publication December 28, 1983. Supported in part with NIH grant #1 P01 AG 03104-02. Presented in part at the annual meeting of the American Society of Anesthesiologists, Atlanta, Georgia, October 1983.

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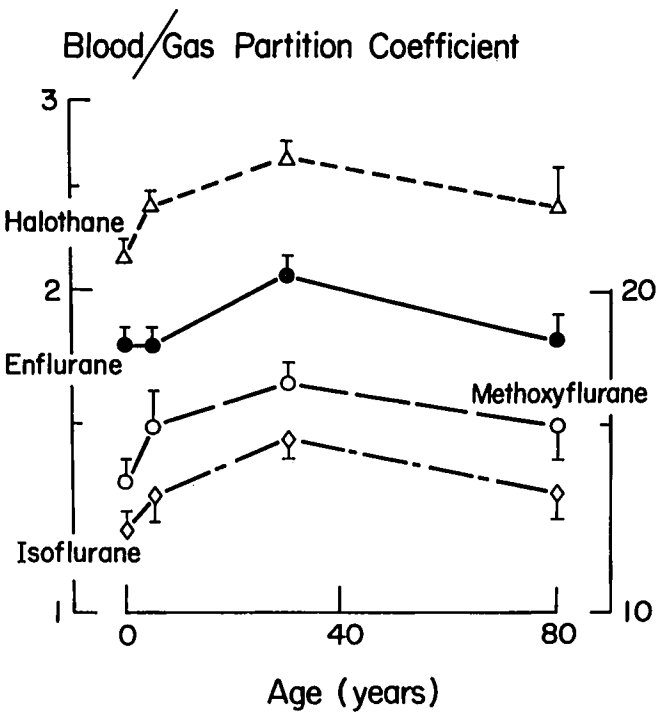

FIG. 1. Relationship between age and the blood–gas partition coefficients of isoflurane, enflurane, halothane, and methoxyflurane. The partition coefficients for newborns (n = 10), children (n = 11), and adults (n = 11) are significantly different ($P < 0.005$) from each other, however, there is no significant difference between the partition coefficients in children and elderly adults (n = 10). There also is no significant difference between the partition coefficients of enflurane in newborns and children. Data are mean ± SD.

of isoflurane, enflurane, halothane, and methoxyflurane, and an 8-ml clotted specimen for determination of the serum albumin, globulin, triglyceride, and cholesterol concentrations. Using a mixture of four anesthetic gases—0.6% isoflurane, 0.6% enflurane, 0.6% halothane, and 0.05% methoxyflurane—we measured the four blood–gas partition coefficients concurrently at 37° C, as described previously.[13]

Statistical significance ($P < 0.05$) was determined by an analysis of variance and the Student–Newman–Keuls multiple range test.[14] Regressions were sought between the blood–gas partition coefficients of each of the four anesthetics and the individual serum albumin, globulin, triglyceride, and cholesterol concentrations using stepwise multiple linear regression analysis.[15]

Results

The blood–gas partition coefficients of isoflurane, enflurane, halothane, and methoxyflurane changed significantly with age (fig. 1). The blood–gas partition coefficients in newborns were 18% lower than those in adults (12% lower for enflurane) ($P < 0.005$); those in children were not different from those in elderly adults; and those in both children and elderly adults were 12% lower than those in adults ($P < 0.005$). The blood–gas partition coefficient of enflurane in newborns was not different from that in children. The partition coefficients for the volunteer and inpatient elderly adults were not different.

The mean ages and mean serum albumin, globulin, triglyceride, and cholesterol concentrations in the four age groups are summarized in table 1. The mean serum albumin concentrations in the three age groups—newborns, children and elderly adults—were significantly less than the mean serum albumin concentration in adults ($P < 0.005$). The mean serum albumin concentration increased with age to a maximum value in adults and then decreased in elderly adults in parallel with the age-related changes in blood–gas partition coefficients of the four anesthetics. The serum globulin, triglyceride and cholesterol concentrations increased progressively with age to a maximum value in elderly adults. Significant regressions, based on the individual subject data, were found between the blood–gas partition coefficients of both isoflurane and enflurane, and the serum albumin, and triglyceride concentrations; between that of halothane and the serum cholesterol, albumin, triglyceride, and globulin concentrations; and between that of methoxyflurane and the serum cholesterol, albumin, and globulin concentrations (table 2). Correlation coefficients (r) for the linear regression equations of the four anesthetics ranged from 0.62 to 0.84 (table 2).

Discussion

The blood–gas partition coefficients of isoflurane, enflurane, halothane, and methoxyflurane are significantly ($P < 0.005$) lower in newborns, children, and elderly adults than in adults. The lower partition coefficients in children explain in part the more rapid rate of rise of alveolar anesthetic partial pressure in children compared with that in adults and account for part of the discrepancy in the rate of rise of alveolar anesthetic partial pressure in children between the results of the mathematical model and the *in vivo* measurements. Furthermore, the lower blood–gas partition coefficients in newborns and elderly adults suggest that the rate of rise of alveolar anesthetic partial pressure in these two age groups may be more rapid than it is in adults.[1–4,16] This latter hypothesis requires further investigation.

The blood–gas partition coefficients of isoflurane, en-

TABLE 1. Summary of the Mean Ages and Blood Chemistry for Four Groups of Subjects

Group	Mean Age (yr)	Albumin (mg/dl)	Globulin (mg/dl)	Triglyceride (mg/dl)	Cholesterol (mg/dl)
Newborns	0	3.74 ± 0.3*	2.11 ± 0.2	40 ± 9	85 ± 17*
Children	5	3.90 ± 0.3*	2.36 ± 0.2	60 ± 20	148 ± 25*
Adults	30	4.50 ± 0.3	2.45 ± 0.2	70 ± 15	195 ± 19
Elderly adults	80	3.80 ± 0.4*	2.90 ± 0.6*	148 ± 90*	197 ± 38

The mean ages and mean blood chemistry values for the 42 subjects in four age groups. The mean serum albumin concentrations parallel the changes in the blood–gas partition coefficients with age suggesting a high correlation between the two parameters. Similar but less dramatic overall correlations hold for the serum triglyceride and the serum cholesterol concentrations.

Data are means ± SD.

* $P < 0.005$ significantly different from respective adult values.

flurane, and halothane in adults agree closely with those reported by other investigators.[10,17–26] However, the partition coefficients for methoxyflurane are approximately 20% greater than those reported previously.[19–21] In a previous study,[13] we determined that after 2 h of incubation, the liquid and gas phases were in equilibrium (*i.e.*, incubation periods longer than 1.5 h did not alter the partition coefficients); that there was no interaction between anesthetics; and that the coefficient of variation of the partition coefficients was less than 6% for the four anesthetics studied. We have no explanation for the greater blood–gas partition coefficients of methoxyflurane. Although our values for methoxyflurane in adults are at the upper limits of the range of other investigators, the relationship between anesthetic solubility and age remains clear.

The blood–gas partition coefficient is an important determinant of the rate of rise of alveolar anesthetic partial pressure and thus, of the speed of induction of anesthesia. The more rapid rate of rise of alveolar anesthetic partial pressure and the more rapid rate of induction of anesthesia in children compared with those in adults may be explained in part by the lower blood–gas partition coefficients in children. However, a lower blood–gas partition coefficient has a dual effect on the rate of induction of anesthesia: it not only accelerates the rate of rise of alveolar anesthetic partial pressure, but it also may slow the rate of rise of tissue anesthetic partial pressure.[4] That is, a lower blood–gas partition coefficient decreases the quantity of anesthetic delivered to tissues per unit blood volume and, therefore, slows the rate of rise of tissue anesthetic partial pressure, unless the tissue–blood partition coefficient decreases in the same proportion as the blood–gas partition coefficient.

We found that the blood–gas partition coefficients in newborns were consistently lower than those in adults by 18% (by 12% for enflurane). Gibbs and co-workers, however, measured the blood–gas partition coefficients in newborns and parturients and found no consistent difference between the two age groups.[25] In their study, the partition coefficients of isoflurane and halothane were lower in newborns than in parturients, whereas that of methoxyflurane was greater in newborns than in parturients. The greater value for methoxyflurane in newborns in their study may have resulted from the use of a high concentration of methoxyflurane (2%). This con-

TABLE 2. Regression and Correlation Coefficients between the Blood–Gas Partition Coefficients (λ) and the Serum Constituents*

	Intercept	Regression Coefficients				Correl Coeff.
		Albumin	Globulin	Triglyceride	Cholesterol	
Isoflurane	0.532	0.178^{1}	—	0.0009^{2}	—	0.72
Enflurane	0.965	0.211^{1}	—	0.0007^{2}	—	0.60
Halothane	1.55	0.205^{2}	-0.188^{4}	0.002^{3}	0.002^{1}	0.82
Methoxyflurane	10.29	1.136^{2}	-1.225^{3}	—	0.020^{1}	0.84

The intercepts (A_0), and regression coefficients (A_{1-4}) for the least squares linear regressions between the blood–gas partition coefficients (λ) and the serum constituents: $\lambda = A_0 + A_1 \times W + A_2 \times X + A_3 \times Y + A_4 \times Z$ where W, X, Y, and Z are the concentrations of serum constituents corresponding to the respective regression coefficients A_{1-4}. The predominance of albumin in the regression equations for isoflurane and enflurane and for both cholesterol and albumin in those equations for halothane and methoxyflurane is apparent.

* — = serum constituent did not contribute significantly to the linear regression analysis; ^{1,2,3,4} superscripts correspond to the statistical priority (1—high priority; 4—low priority) given to the serum constituents that were included in the regression analysis for each partition coefficient.

centration, which approaches the saturation vapor pressure of methoxyflurane (22.8 mmHg), is capable of denaturing proteins and altering lipid binding sites, thereby changing the solubility of methoxyflurane in blood. It is unclear why the blood of newborns may be more susceptible to this effect than that of parturients. Alternatively, pregnancy, in some unknown fashion, may decrease the solubility of methoxyflurane in blood.

Based on the regression analysis, we found that two or more serum constituents are required to predict the blood–gas partition coefficients of isoflurane, enflurane, halothane, and methoxyflurane over the range of ages studied (table 2). Because the concentrations of all four serum constituents in this study increased with age, we could not identify any one serum constituent that singularly determined the blood–gas partition coefficients. Previously, however, Saraiva *et al.* found that the serum triglyceride concentration singularly predicted the blood–gas partition coefficient of halothane.[10] The range of serum triglyceride concentrations in Saraiva's study was far greater than the range of concentrations of the other serum constituents, and as a result, a higher correlation coefficient would be expected between the blood–gas partition coefficients and the serum triglyceride concentration than between the partition coefficients and the other serum constituents.

Pang and co-workers found that in blood containing normal concentrations of most serum constituents (except cholesterol-0 mg/dl), three times as much halothane is transported by albumin than is transported by triglycerides.[9] Their work supports previous studies[8] in which albumin was found to be an important determinant of anesthetic solubility. The regression analyses in this study suggest a primary role for albumin in determining the blood–gas partition coefficients of isoflurane and enflurane and a secondary role for albumin in determining the partition coefficients of halothane and methoxyflurane (table 2).

We did not include hematocrit in the linear regression analysis because previous studies failed to clearly define significant relationships between hematocrit and the blood–gas partition coefficients of isoflurane, enflurane, halothane, and methoxyflurane. The effect of hematocrit on the blood–gas partition coefficient of halothane is unclear because of the widely divergent effects reported.[8–10,18,21,27] Furthermore, few studies have documented the effects of hematocrit on the blood–gas partition coefficients of isoflurane, enflurane, and methoxyflurane.[21,25,28] Thus, based on the current data available, hematocrit was not included in the regression analysis.

In summary, we found that age significantly ($P < 0.005$) affects the blood–gas partition coefficients of isoflurane, enflurane, halothane, and methoxyflurane and that this effect may explain in part the more rapid rise of alveolar anesthetic partial pressure in infants and children compared with that in adults. The partition coefficients in newborns were 18% lower than those in adults ($P < 0.005$), and those in both children and elderly adults were 12% lower than those in adults ($P < 0.005$). The blood–gas partition coefficients of the four anesthetic agents correlated with two or more serum constituents.

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