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Kinetics of Desflurane, Isoflurane, and Halothane in Humans

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The low solubility of desflurane in blood and tissues suggests that the partial pressures of this agent in blood and tissues should approach the inspired partial pressure more rapidly than would the blood and tissue partial pressures of other potent inhaled anesthetics. We tested this prediction, comparing the pharmacokinetics of desflurane with those of isoflurane, halothane, and nitrous oxide in eight volunteers. We measured the rate at which the alveolar (end-tidal) (FA) concentration of nitrous oxide increased towards an inspired (FI) concentration of 65–70%, and then measured the concurrent increase in FA and mixed expired concentrations (FM) of desflurane, isoflurane, and halothane at respective FI values of 2.0%, 0.4%, 0.2%. Minute ventilation ($\dot{V}_E$) was measured concurrently with the measurements of anesthetic concentrations. The potent vapors were administered for 30 min; administration of nitrous oxide continued throughout the period of anesthesia. For the potent agents, we also measured $\dot{V}_E$, FA, and FM for 5–7 days of elimination. We used FA/FI and FA/FA$_0$ (FA$_0$ = the last FA during the administration of each anesthetic) to define the rate of increase of anesthetic in the lungs and the rate of elimination of anesthetic, respectively. FA/FI values at 30 min of administration were: (mean ± SD) nitrous oxide 0.99 ± 0.01, desflurane 0.90 ± 0.01, isoflurane 0.73 ± 0.03, and halothane 0.58 ± 0.04. FA/FA$_0$ values after 5 min of elimination were: desflurane 0.14 ± 0.02, isoflurane 0.22 ± 0.02, and halothane 0.25 ± 0.02. Recovery (volume of anesthetic recovered during elimination per volume taken up) of desflurane (105 ± 25%) equalled recovery of isoflurane (102 ± 13%) and exceeded recovery of halothane (64 ± 9%). Time constants for a five-compartment mammillary model for halothane and isoflurane differed for the lungs, fat group, and hepatic metabolism, and exceeded those for desflurane for all compartments. In summary, we found that FA/FI of desflurane increases more rapidly and that FA/FA$_0$ decreases more rapidly in humans than do these variables with other available potent anesthetics. We also found that desflurane resists biodegradation in humans and so may have little or no toxic potential. (Key words: Anesthetics, Gases: Nitrous oxide. Anesthetics, volatile: desflurane; isoflurane; halothane. Pharmacokinetics, volatile agents.)

THE SMALLER (0.42) blood–gas partition coefficient[1] and tissue–blood partition coefficients[2] of desflurane compared to those of isoflurane and halothane indicate a more rapid increase in the rate of rise of anesthetic in the lungs (FA/FI) and a more rapid decrease in the rate of elimination (FA/FA$_0$) with desflurane than with more soluble agents such as isoflurane and halothane (where FA = alveolar [end-tidal] concentration; FI = inspired concentration; and FA$_0$ = the last FA during administration of anesthetic). A short-term (30-min) study of these values during administration and elimination of subanesthetic concentrations of desflurane in volunteers produced results qualitatively consistent with the low solubility of desflurane.[3] The kinetics of isoflurane and halothane may also be predicted from their respective solubilities in blood, except that metabolism accelerates the terminal elimination of halothane.[4] Studies of fluoride serum concentrations and excretion in enzyme-induced rats indicate that desflurane undergoes minimal metabolism, compared with that of isoflurane, halothane, or methoxyflurane.[5] Similarly, fluoride levels increase minimally or not at all after prolonged anesthesia with desflurane in swine.[6] Therefore, metabolism of desflurane should neither limit FA/FI nor accelerate the decrease in FA/FA$_0$.

Combined, this evidence suggests that the rates of change in FA/FI and FA/FA$_0$ with desflurane should exceed those with isoflurane or halothane. However, no data directly support (or refute) this premise.

Existing data also suggest that studies of mass balance should show that recovery of desflurane (as a percentage of the volume of desflurane taken up) equals or exceeds that of isoflurane and that recovery of either should exceed recovery of halothane. However, a preliminary study of these characteristics for all three agents in swine did not show more recovery of desflurane than of halothane[7]; moreover, recovery of desflurane was significantly less than that for sevoflurane, an agent known to be metabolized to inorganic fluoride.[8]

To better define the relative metabolism and other pharmacokinetic characteristics of desflurane, isoflurane, and halothane in humans, we investigated the simultaneous FA/FI and FA/FA$_0$ values for these anesthetics. We conducted a mass balance study to determine whether the low concentrations of fluoride in plasma and urine after anesthesia with desflurane reflect minimal metabo-

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lism. Finally, we compared the FA/FI of desflurane with that of nitrous oxide, an anesthetic with a nearly identical blood–gas partition coefficient.[9]

Materials and Methods

With approval from the University of California, San Francisco Committee on Human Research and informed consent from the subjects, we studied eight healthy male volunteers (age 25 ± 5 yr (mean ± SD); body weight 76 ± 7 kg; height 182 ± 4 cm). An 18-G intravenous catheter was inserted and lactated Ringer's solution was administered at 100–150 ml/h. Anesthesia was induced by intravenous injection of midazolam 0.1–0.2 mg/kg and/or thiopental 4–8 mg/kg and fentanyl 2–5 μg/kg. After oxygenation *via* mask, vecuronium 0.12–0.14 mg/kg was administered intravenously to facilitate tracheal intubation. Ventilation was controlled *via* a nonrebreathing system to produce normocapnea (end-tidal carbon dioxide of 5.5–6.5%), and thereafter, 70% nitrous oxide was administered for 30 min with inspired and end-tidal concentrations of nitrous oxide and carbon dioxide measured by mass spectrometry and recorded. After the 30 min of administration of nitrous oxide, basal anesthesia was maintained with 65% nitrous oxide supplemented with intravenous administration of midazolam and fentanyl, as indicated by blood pressure and heart rate. Blood pressure and heart rate were measured noninvasively by an oscillometric method (Dinamap®). Paralysis was maintained by intravenous administration of vecuronium as indicated by train-of-four response to electrical stimuli of the ulnar nerve. Esophageal temperature was monitored and maintained at 36.5–37° C using a Bair Hugger® forced-air warmer.

Cylinders containing a mixture of 2.0% desflurane, 0.4% isoflurane, and 0.2% halothane, balance 35% oxygen/65% nitrous oxide, were prepared. Soon after the 30-min administration of nitrous oxide, this mixture of volatile agents was administered for 30 min *via* a nonrebreathing circuit. The expiratory limb of the circuit was composed of corrugated Teflon® tubing connected to a 1-l aluminum mixing chamber (to mix alveolar and dead-space gases and thereby supply a mixed expired sample) having a port for sampling of mixed expired (FM) gas. The output from the mixing chamber was connected to a spirometer. End-tidal gas was sampled from a port at the tracheal tube. A small (about 50-ml) dead space composed of corrugated Teflon® tubing was interposed between this sampling site and the connection to the nonrebreathing valve. The dead space served to protect the end-tidal sample from contamination with inspired gas. Inspired gas was collected from a port on the nonrebreathing valve just before the valve assembly.

To define the pharmacokinetics of the potent agents during their early administration, end-tidal samples were collected from the first five breaths, and then from breaths at 0.75, 1, 1.5, 2, 3, 5, 7.5, 10, 12.5, 15, 20, 25, and 29 min. Minute ventilation ($\dot{V}_E$) was measured and mixed expired and inspired samples were collected at 5, 7.5, 10, 12.5, 15, 20, 25, and 29 min. Precisely at 30 min, administration of the volatile anesthetics was discontinued, and the breathing circuit was exchanged with a fresh inspiratory and expiratory circuit. A basal level of anesthesia was continued with 65% nitrous oxide, midazolam, fentanyl, and vecuronium. End-tidal gas samples were collected from the first five breaths and then from breaths at 0.75, 1, 1.5, 2, 3, 5, 7.5, 10, 12.5, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 180, 210, 240, 300, 400, 500, 600, 800, and 1,400 min and on each morning thereafter for 5–7 days. Ventilation and mixed expired and inspired samples were measured at 5, 7.5, 10, 12.5, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 180, 210, 240, 300, 400, 500, 600, and 1,400 min and on each morning thereafter for 5–7 days. After 150 min of elimination, the administration of the basal anesthesia was discontinued, and the elimination of nitrous oxide was measured for 10 min, or for a shorter period if the subject coughed or moved. The endotracheal tube was then removed. Thereafter, gas samples were collected through a mouth piece and a low resistance nonrebreathing valve connected by Teflon® tubing to a mixing chamber (as described earlier) and a spirometer. Nose clips were used to prevent breathing through the nose. All gas samples were obtained in 50-ml glass syringes sealed with nylon three-way stopcocks. The syringes were stored upright until the gas contents were analyzed.

All samples were analyzed for anesthetic concentrations by gas chromatography. We used two Gow-Mac Series 580 flame ionization detector gas chromatographs equipped with a 6-m long, stainless steel column (3 mm in diameter) packed with Chromosorb-WHT 60–80 mesh maintained at 48° C. A nitrogen carrier stream flowing at 6 ml/min was delivered through the column to a flame ionization detector at 150° C, supplied by hydrogen at 10 ml/min and by air at 200 ml/min. One chromatograph was equipped with a 0.1-ml sample loop for high concentrations, and the other with a 1.0-ml sample loop for lower concentrations. Results were recorded on a strip recorder. The chromatographs were calibrated using secondary tank standards that had been calibrated with primary standards produced by injection of a liquid aliquot of each anesthetic by micropipette into a flask of known volume. Peak heights were proportional to concentration over the entire range of concentrations studied, and linearity of the gas chromatographs was confirmed over the range of concentrations measured. Secondary anesthetic standards

(prepared in tanks and calibrated against primary volumetric standards), injected every 1–2 h, normally did not vary more than 2% on a given day. The minimum signal-to-noise ratio (obtained on the last day of sampling) was 3–4.

Values for FM during the first 3 min were estimated using the following formula:

$$FM = fA \times FA + fD \times FI$$

where fA = the fraction of ventilation coming from the alveoli and fD = the fraction of ventilation coming from the dead space. The average values for fA and fD calculated from the 10-, 15-, and 20-min samples were obtained using this same formula (*i.e.*, substitute [1 − fA] for fD to solve for fA, and substitute [1 − fD] for fA to solve for fD).

As noted earlier, the ratio of FA to FI (FA/FI) was used to define the pharmacokinetics of each anesthetic during its administration. The ratio of FA to FA_0 (FA/FA_0) was used to define the pharmacokinetics during elimination, where FA_0 is the alveolar concentration of anesthetic found immediately before administration was discontinued. The FA/FI and FA/FA_0 at each time point were compared among the anesthetics using a paired *t* test with Bonferroni correction for multiple comparison.[10]

Multiexponential (multicompartment) functions of the form

$$\sum_{i=0}^{n} A_i e^{-\lambda_i t}$$

were fit to the elimination data using least-squares analysis.[11,12] We will refer to this analysis as the "hybrid" analysis to distinguish it from a second analysis (see below) that we will refer to as the "mammillary" analysis. The coefficient A_i has no units; λ_i has units of reciprocal time (in this case, min^{-1}); and *t* is time (min). We fit equations (functions or models) having successively more exponents (interpreted as compartments) to the data for each anesthetic for each subject (*i.e.*, for each of the 24 data sets that we obtained from three potent agents given to eight subjects). For each data set, the model having the greatest number of compartments (highest n) that significantly decreased the residual sum of squares when compared with the model having one less compartment (n − 1) was considered to provide the "best fit" ($P < 0.05$, F-ratio test).[13]

Hybrid time constants were calculated from the rate constants (λ_i) as $1/\lambda_i$ for each compartment. The time constants for five-compartment models were compared among the three potent agents. The significance of any difference was assessed using analysis of variance with repeated measures and the Student-Newman-Keuls method of multiple comparison.[14]

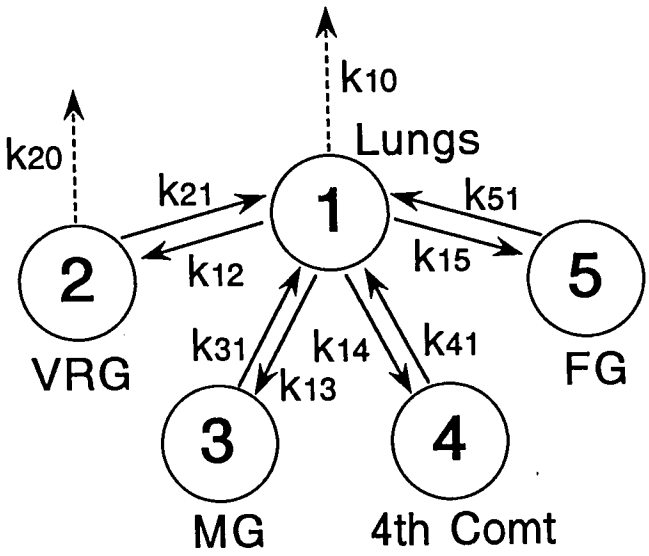

FIG. 1. The five-compartment function (or model) used in determining the values for the mammillary model. Compartments 1 through 5 represent the central compartment, the vessel-rich group (VRG), the muscle group (MG), the fourth compartment (4th compt), and the fat group (FG), respectively. k_{10} and k_{20} represent pulmonary elimination and hepatic metabolism, respectively.

We also calculated rate constants for these data sets using a five-compartment mammillary model (fig. 1). This model was fit simultaneously to the logarithm of the concentration of potent agents in end-tidal gas (FA) and the logarithm of the rate of excretion of the potent agents *via* the lungs for each subject by using five differential equations to describe the rate of change in anesthetic concentration in each compartment. A method involving the matrix exponential (the matrix exponential is equivalent in its result to a differential equation solver) was used to effectively integrate the differential equations. ‡‡Fitting the excretion data simultaneously enabled us to estimate the mammillary rate constant for anesthetic metabolism in the second compartment (the vessel-rich group, containing the liver). These data analyses yielded estimates of the volume of the central compartment (V_1) and mammillary rate constants: the elimination rate constants k_{10} and k_{20}, and the intercompartmental transfer rate constants, k_{1j} and k_{j1} (where $j = 2, \ldots, 5$) (fig. 1). Elimination of anesthetics was permitted from two sites: the central compartment (lungs: k_{10}) and the second compartment (vessel-rich group: k_{20}). These sites were chosen because the volatile anesthetics are eliminated from the body primarily by exhalation and metabolism (*via* the liver). From the mammillary rate constants, we calculated mammillary

‡‡ Beal SL, Sheiner LB: NONMEM Users Guide IV. San Francisco, Regents of the University of California, 1984, pp 55.

transit times [$1/k_{10} + k_{12} + k_{13} + k_{14} + k_{15}$), $1/(k_{20} + k_{21})$ and $1/k_{j1}$ (where $j = 3, 4, 5$)]. Transit times for $1/k_{j1}$ also equal the time constants for the respective compartments. Time constants for the central compartment ($1/k_{10}$) and elimination from the vessel rich group ($1/k_{20}$) also were calculated.

We know that the compartments of the mammillary models do not always translate into anatomic tissue compartments. However, for the volatile anesthetics, considerable information is available regarding their partition characteristics and the sites and magnitudes of metabolism. We also know that inhaled anesthetics do not bind appreciably to the tissues of the body.[15,16] Based on these data, one may speculate on the identity of the compartments of the mammillary models. Assuming that the delivery of anesthetic to the tissues is perfusion- and not diffusion-limited, the mammillary rate constants may be used to estimate tissue blood flows and tissue volumes.[17] The results of this speculation then may be compared with the known physiologic and anatomic characteristics of the tissue compartments. The validity of this speculation may be judged by the correspondence of the estimates of blood flows and tissue volumes with known values for these characteristics.

To make this speculation requires knowing the anesthetic's tissue–blood and tissue–gas partition coefficients for the particular tissue group. For this analysis, we assumed that the second-, third-, and fifth-compartment tissues were the vessel-rich group (VRG), the muscle group (MG), and fat group (FG) respectively. We assumed that the fourth compartment also was fat. To estimate flow (milliliters perfusion per 100 milliliters tissue per minute) for any tissue group (*e.g.*, the *j*th tissue group), we multiplied the tissue–blood partition coefficient (which we have determined previously[2]) by the corresponding calculated mammillary rate constant value (*i.e.*, k_{j1}, where $j = 2, \ldots, 5$) and by 100. To estimate the volume for each tissue, we multiplied the estimate of the volume of the central compartment by the ratio of the ingress and egress mammillary rate constants (*i.e.*, k_{1j}/k_{j1} [where $j = 3, 4, 5$] and $k_{12}/[k_{20} + k_{21}]$ for the vessel rich tissues) and divided the resulting number by the tissue–gas partition coefficient.

For each subject, total body clearance for desflurane, isoflurane, and halothane was calculated by dividing the doses of the anesthetics delivered to the alveoli (calculated as $F_I \times \dot{V}_A \times 30$ min, where $\dot{V}_A = f_A \times \dot{V}_E$) by the area under the alveolar administration and elimination curves. We estimated the area under the alveolar concentrations of anesthetics against time by the trapezoidal rule. The area under the elimination curve from the last data point to time infinity was calculated by taking the ratio of the last alveolar concentration of anesthetic and the estimate of the terminal hybrid rate constant. These data were tested for differences in total body clearance among the anesthetics using analysis of variance with repeated measures and the Student-Newman-Keuls test for multiple comparisons.[14]

We assessed the total pulmonary uptake and elimination of the potent anesthetics as follows. Uptake and elimination rates were calculated for each anesthetic at each time point. Uptake rates were calculated as $\dot{V}_E \times (F_I - F_M)$. Elimination rates were calculated as $\dot{V}_E \times F_M$. Total uptake for each anesthetic was estimated as the area under the curve generated by plotting the anesthetic uptake rate against time (trapezoidal method). Total recovery of unchanged anesthetic in exhaled gases (*i.e.*, elimination by ventilation) (mass balance) was calculated by the same method, and terminal recovery was estimated by multiplying the elimination rate at the final time point by the terminal hybrid time constant (determined separately for each anesthetic in each subject, as described earlier). Percent recovery (*i.e.*, the percentage of anesthetic taken up that is eliminated by ventilation) of each anesthetic was calculated as the total recovery divided by the total uptake, and multiplied by 100.

These mass balance data then were used to determine the extent of desflurane, isoflurane, and halothane metabolism. We assumed that isoflurane was not metabolized and that the percent recovery of isoflurane might differ from 100% because of other sources of anesthetic loss (*e.g.*, through the skin and in the urine), or because of inconsistencies in ventilation and circulation (*e.g.*, our measurements always were taken with volunteers at or near basal state; however, after release form the hospital [after 1,400 min] subjects pursued normal activities, likely exceeding basal levels for at least a fraction of each day). We also assumed that other sources of anesthetic loss or inconsistencies in ventilation or circulation would affect the recovery of each anesthetic proportionately. To compensate for these losses, we calculated not only the absolute percent recovery of each anesthetic but also the percent recovery of each anesthetic normalized to that of isoflurane (the latter by dividing the percent recovery of the anesthetic by the percent recovery of isoflurane.) Deficits in percent recovery were assumed to be due to metabolism. Differences among anesthetics were analyzed by parametric and/or nonparametric analysis of variance with repeated measures and the Student-Newman-Keuls test for multiple comparisons.[14] For all measurements we accepted $P < 0.05$ as significant.

Results

F_A/F_I increased more rapidly with nitrous oxide than with desflurane, whereas F_A/F_{A_0} decreased more rapidly with desflurane (figs. 2–4). F_A/F_I increased and F_A/F_{A_0}

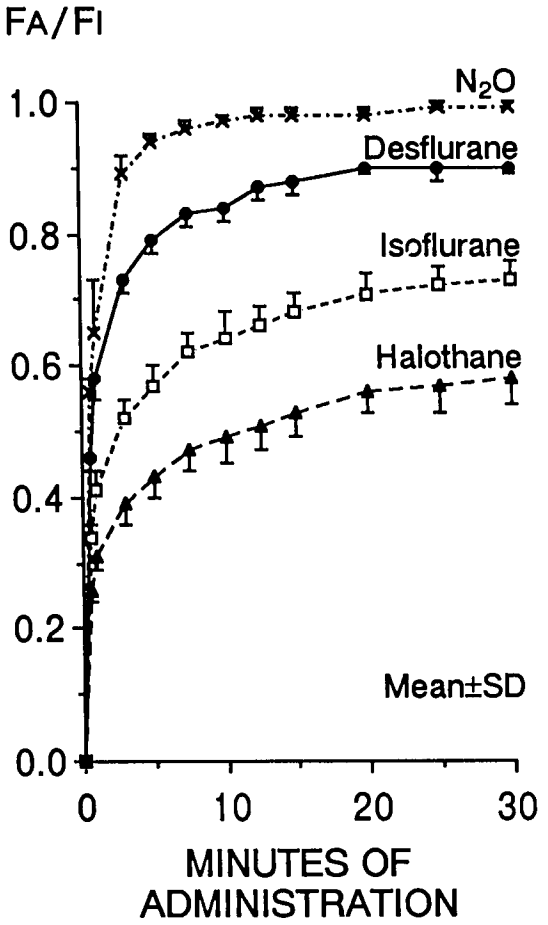

FIG. 2. The pharmacokinetics of desflurane, isoflurane and halothane during administration of these agents are defined as the ratios of end-tidal anesthetic concentrations (FA) to inspired anesthetic concentrations FI (*i.e.*, FA/FI) (mean ± SD). Consistent with the lower blood–gas partition coefficient of desflurane the increase in FA/FI for this anesthetic is faster than is that of isoflurane and halothane. The increase in FA/FI of nitrous oxide is faster than with desflurane because of the concentration effect.

decreased more rapidly with desflurane than with isoflurane and halothane; all FA/FA_0 values for desflurane were less than those for isoflurane and halothane, after the first three breaths. FA/FI increased more rapidly with isoflurane than with halothane, but except for the first 25 min of elimination, FA/FA_0 of isoflurane did not differ from that of halothane.

All 24 data sets of FA/FA_0 values fit best to a five-compartment hybrid model. Following the suggestion of Carpenter *et al.*,[4] we interpreted the first, second, third, fourth, and fifth compartments as representing the lungs, the VRG, the MG, a layer of fat that receives anesthetic from adjacent vessel-rich organs by intertissue diffusion (fourth compartment), and the FG, respectively. Values for A_1 tended to be larger for desflurane, whereas values for A_2 through A_5 tended to be larger for isoflurane and halothane (table 1). Note that the A_i values do not lend themselves to a simple interpretation because they are complex functions incorporating all of the other rate constants, particularly the adjacent constants. Desflurane time constants were smaller than those for isoflurane and halothane for all compartments except the lungs (table 2). The hybrid time constants for isoflurane were smaller than those for halothane for the fourth compartment and the FG. The coefficients of variation for the values for A_i and λ_i (describing the intercepts and slopes for the five compartments of the model) were of limited size. For the total of 30 average values from the eight subjects (10 for each of three anesthetics), they ranged (mean ± SD) from

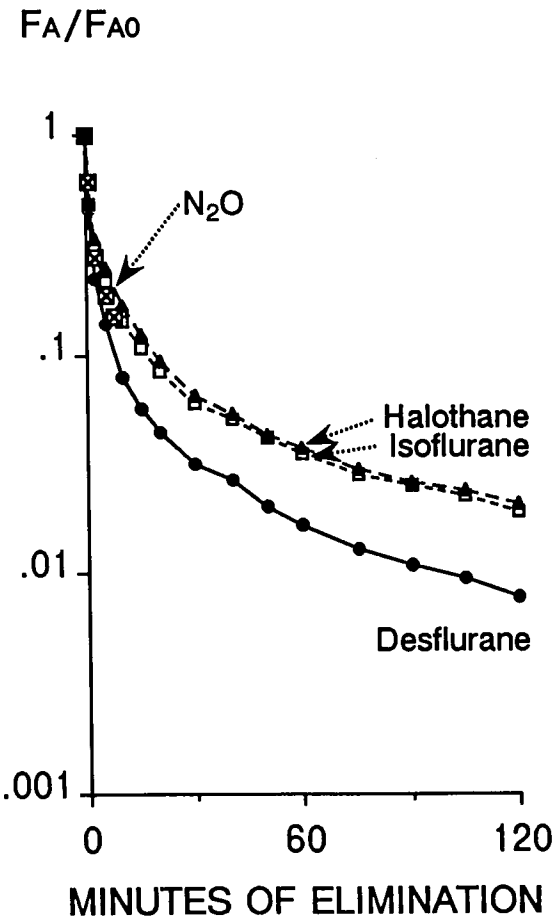

FIG. 3. Elimination of desflurane, isoflurane, and halothane is defined as the ratio of end-tidal anesthetic concentration (FA) to the last FA during administration and immediately before the beginning of elimination (FA_0) (*i.e.*, FA/FA_0). Over this 120-min period, the elimination of desflurane is faster than that of isoflurane and halothane by a factor of 2–2.5 (note the logarithmic scale for the ordinate). Elimination of nitrous oxide is slower (N equals only two) than with desflurane because equilibration with nitrous oxide had continued for an 8–10-fold longer period. Elimination of halothane is slower than that of isoflurane for about 20 min, but by 25 min, the rates of elimination are equal.

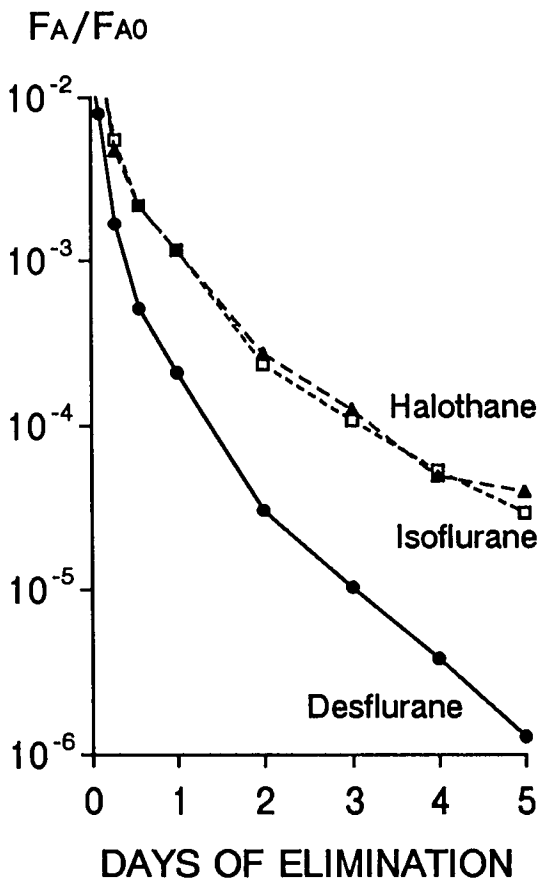

FIG. 4. The terminal elimination of desflurane is faster than that of isoflurane and halothane. After 2–5 days, there is a 10–20-fold difference between the F_A/F_{A_0} values for desflurane and those for halothane or isoflurane.

a low of 4.2 ± 2.5% to a high of 26.0 ± 17.3%. The mean for the 15 averages for the intercepts was 14.2 ± 5.2% and for the 15 averages for the slopes was 12.3 ± 4.8%.

The volume of the central compartment (V_1) increased significantly, as follows: desflurane (2.22 ± 0.48 1) < isoflurane (2.98 ± 0.64 1) < halothane (3.47 ± 0.74 1). Elimination rate constants from the central compartment (k_{10}) decreased significantly, as follows: desflurane > isoflurane > halothane (table 3). Pulmonary elimination clearances, defined as $V_1 \times k_{10}$, were not different among desflurane (4.11 ± 0.45 1/min), isoflurane (3.94 ± 0.34 1/min), and halothane (3.94 ± 0.33 1/min). Rate constants from the central compartment to the VRG (k_{12}), MG (k_{13}), fourth compartment (k_{14}), and the FG (k_{15}) increased as: desflurane < isoflurane < halothane, except for the fourth compartment and the FG, where the rate constants for isoflurane and halothane were not different. Desflurane rate constants from the peripheral compartments to the central compartment exceeded those for isoflurane and halothane for all peripheral compartments. All three agents differed significantly in elimination rate constants (k_{20}) from the VRG (liver).

Desflurane mammillary time constants and transit times were smaller than those for isoflurane and halothane (table 4). Elimination time constants from the VRG ($1/k_{20}$) differed among anesthetics. Because these data were skewed, comparisons were made using a nonparametric analysis of variance with repeated measures (rank test).[18]

The calculated blood flows for a given compartment did not differ among anesthetics (table 5). However, some differences appeared in the calculated tissue volumes: desflurane had larger volumes than halothane for all compartments except fat (FG). Desflurane also had larger VRG and fourth compartments than isoflurane. Isoflurane had larger MG and fourth compartment volumes than did halothane. Total body clearance of desflurane (4.6 ± 0.9 1/min) and halothane (4.8 ± 0.51/min) were significantly greater than that of isoflurane (4.0 ± 0.51/min).

The recovery of desflurane and isoflurane did not differ from each other or from 100%, and recovery of halothane was significantly less than that of desflurane and isoflurane (table 6).

Discussion

F_A/F_I of desflurane increased more rapidly than that of either isoflurane or halothane (fig. 2). These results agree with what would be predicted from the relative solubilities of these anesthetics. They also suggest that induction of anesthesia with desflurane may be more rapid than that with the other agents, if pungency does not

TABLE 1. A_i Coefficients × 100

Coefficient	Compartment	Desflurane	Isoflurane	Halothane
A_1	Lungs	64.4 ± 4.8*	57.2 ± 3.6*	53.7 ± 3.0*
A_2	Vessel-rich group	22.5 ± 3.8*	28.4 ± 3.4*	33.6 ± 3.6*
A_3	Muscle group	4.86 ± 1.92	5.93 ± 2.09	5.94 ± 0.69
A_4	Fourth compartment	0.775 ± 0.482	1.125 ± 0.669	0.830 ± 0.406
A_5	Fat group	0.031 ± 0.029†	0.080 ± 0.042	0.067 ± 0.040

Values are mean ± SD and have no units.
* Significantly different from the other anesthetics ($P < 0.05$).
† Significantly different from isoflurane and halothane ($P < 0.05$).

TABLE 2. Hybrid (Washout) Time Constants

Compartment	Desflurane	Isoflurane	Halothane
Lungs	0.441 ± 0.042*	0.380 ± 0.058*	0.308 ± 0.070*
Vessel-rich group	5.78 ± 1.64†	8.72 ± 2.12	9.34 ± 1.16
Muscle group	48.9 ± 21.7†	80.0 ± 26.0	84.6 ± 14.2
Fourth compartment	300 ± 107*	482 ± 127*	551 ± 123*
Fat group	1350 ± 230*	2110 ± 320*	2550 ± 370*

Values are mean ± SD; units are minutes.
* Significantly different from the other anesthetics ($P < 0.05$).
† Significant vs. isoflurane and halothane ($P < 0.05$).

limit the rate at which the inspired concentration of desflurane may be increased.

However, FA/FI increased more rapidly with nitrous oxide than with desflurane, despite the near equivalence of their solubilities in blood. Differences in tissue solubility (nitrous oxide is modestly less soluble in tissues) may explain a small part of this difference, but the greater part is due to the concentration effect,[19] a factor that effectively decreases the blood solubility of nitrous oxide by 70%.[20] Thus, although nitrous oxide has limited anesthetic potency, the effect of a given concentration will be achieved more rapidly with it than with desflurane.

FA/FA_0 of desflurane also decreased more rapidly than that of either isoflurane or halothane (figs. 3 and 4). Again, this finding is consistent with the lesser solubility of desflurane in blood[1] and tissues[2] and indicates that recovery from anesthesia with desflurane will be more rapid than will recovery from isoflurane or halothane. The more rapid equilibration of desflurane with tissues is evident in its shorter hybrid and mammillary time constants, a finding also consistent with its lower tissue/blood partition coefficients. Studies in rats also demonstrate more rapid recovery.[21]

Our results also have implications for long-term recovery. In the first 30 min of recovery, FA/FA_0 for desflurane was half that of either isoflurane or halothane. Over the next several days, this relative difference increased further (fig. 4): by day 2 it exceeded by a factor of 10 and by day 5 by a factor of 20. If low-to-trace levels of anesthetic agents affect mental function or influence metabolism and toxicity, the residual effects of desflurane will be an order of magnitude less than those of anesthesia with isoflurane or halothane (assuming that the potency of trace levels is proportional to anesthetic potency).

Although halothane is more soluble than isoflurane in blood, FA/FA_0 decreased at the same pace for both agents (figs. 3 and 4). These results confirm those of Carpenter *et al.*,[22] who explained this finding as a consequence of metabolism of halothane. Isoflurane leaves the body only *via* the lungs, whereas halothane exits *via* both the lungs and liver. As indicated by our results (which confirm the results of other investigators[22–24]), perhaps 40% of halothane is eliminated *via* the liver (table 6), and this additional pathway compensates for halothane's greater blood solubility.

In contrast to the relationship of FA and FA_0 during administration, FA/FA_0 for desflurane decreased more rapidly than that for nitrous oxide (fig. 2). A roughly equal rate of decrease might have been predicted from the equality of the blood–gas partition coefficients for these two agents and the absence of the equivalent of the concentration effect on elimination. Indeed, the decrease of FA/FA_0 of nitrous oxide found by other investigators is similar to the decrease that we found for desflurane.[25–28]

TABLE 3. Mammillary Rate Constants

Rate Constant	Desflurane	Isoflurane	Halothane
k_{10}	1.89 ± 0.29*	1.38 ± 0.25*	1.18 ± 0.23*
k_{12}	0.776 ± 0.249*	1.28 ± 0.30*	2.16 ± 0.47*
k_{13}	0.197 ± 0.041*	0.340 ± 0.059*	0.411 ± 0.061*
k_{14}	0.129 ± 0.039†	0.248 ± 0.083	0.252 ± 0.131
k_{15}	0.0204 ± 0.0126†	0.0610 ± 0.0372	0.0716 ± 0.0376
k_{21}	0.262 ± 0.081†	0.180 ± 0.059	0.168 ± 0.043
k_{31}	0.0282 ± 0.0081†	0.0175 ± 0.0052	0.0169 ± 0.0030
k_{41}	0.00400 ± 0.00126†	0.00249 ± 0.00075	0.00219 ± 0.00038
k_{51}	0.000766 ± 0.000137†	0.000482 ± 0.000050	0.000415 ± 0.000078
k_{20}	0.0092 ± 0.0182*	0.0204 ± 0.0156[a]	0.0456 ± 0.0088*

Values are mean ± SD; units are $minutes^{-1}$.
* Significantly different from the other anesthetics ($P < 0.05$).
† Significantly different from isoflurane and halothane ($P < 0.05$).

TABLE 4. Mammillary Time Constants and Transit Times

Time Constant or Transit Time	Desflurane	Isoflurane	Halothane
$1/k_{10}$ (lungs)	0.540 ± 0.087*	0.755 ± 0.137*	0.879 ± 0.165*
$1/(k_{10} + k_{12} + k_{13} + k_{14} + k_{15})$	0.341 ± 0.059*	0.314 ± 0.062*	0.253 ± 0.047*
$1/k_{21}$ (vessel-rich group)	4.21 ± 1.60†	6.30 ± 2.78	6.31 ± 1.70
$1/(k_{20} + k_{21})$	3.88 ± 0.93†	5.38 ± 1.66	4.86 ± 1.02
$1/k_{31}$ (muscle group)	37.9 ± 10.1†	62.9 ± 21.9	61.0 ± 12.1
$1/k_{41}$ (fourth compartment)	273 ± 88†	435 ± 131	471 ± 102
$1/k_{51}$ (fat group)	1340 ± 230*	2090 ± 230*	2480 ± 440*
$1/k_{20}$	7,500,000 ± 4,630,000‡	126 ± 160‡	23 ± 5‡

Values are mean ± SD; units are minutes.
* Significantly different from the other anesthetics ($P < 0.05$).
† Significantly different from isoflurane and halothane ($P < 0.05$).
‡ Significantly different from the other anesthetics (using nonparametric analysis of variance) ($P < 0.05$).

However, we administered nitrous oxide for a longer period of time than desflurane, and this longer time of equilibration produced greater tissue stores, thereby slowing the decrease of F_A/F_{A_0} of nitrous oxide.

The equivalent rates of decrease of F_A/F_{A_0} of nitrous oxide and desflurane also support the contention that recovery from anesthesia with desflurane will be rapid in humans. However, two reasons suggest that recovery after anesthesia with desflurane is not apt to be quite as rapid as with nitrous oxide. First, desflurane is more potent and may be used to achieve deeper levels of anesthesia. This deeper level of anesthesia from which elimination begins will tend to delay recovery.[29] Second, the tissue–blood partition coefficients for desflurane[2] are greater than those for nitrous oxide,[29–31] and this will proportionately delay clearance of desflurane from the tissues, including the brain.

Both our "raw" and our normalized data for recovery of desflurane in humans indicate minimal or no metabolism of this agent. This finding is consistent with the minimal recovery of fluoride after anesthesia with desflurane (*vs.* isoflurane and halothane) in rats[5] and (*vs.* isoflurane) in swine.[6] Our finding of complete recovery of desflurane eliminates an alternative explanation for the minimal recovery of fluoride—that the metabolites are tightly bound to tissues. Our data differ from those obtained in swine, in that in swine we found no statistically significant difference in the recoveries of desflurane and halothane.[7] However, the trends were the same both in swine and in humans (a greater recovery with desflurane), and we believe that the difference resulted from a greater variability in the data from the studies in swine.

The reader may ask why we undertook both the hybrid and mammillary analyses. We reply that although the analyses overlap in some of the answers they provide, each supplies some unique insights. The mammillary analysis provides the rate constants that (as noted), with a knowledge of partition coefficients, allow estimates of tissue volumes, blood flows, and metabolism. The volumes and flows of the presumed tissue groups may be compared with known values to support the assignment of compartments to specific tissue groups. The hybrid analysis also has some appreciable advantages. It is easier to perform and is more robust. Although not a problem in the current study, in previous instances in which we were unable to obtain convergence with the mammillary analysis, we succeeded using the hybrid analysis. The hybrid analysis provides an economical approach (using appreciably less computer time) to defining the least number of compartments best representing the data. It provides an accurate assessment of the terminal time constant used for extrapolation to infinity. It allows a comparison with historic data (*e.g.*, our results for the hybrid time constants for isoflurane and halothane are similar to those from the studies by Carpenter *et al.*[22] (table 2).

Moreover, the time constants obtained with hybrid

TABLE 5. Estimated Blood Flow and Tissue Volume

Compartment	Blood Flow (ml·100 ml tissue^{-1}·min^{-1})			Tissue Volume (l)		
	Desflurane	Isoflurane	Halothane	Desflurane	Isoflurane	Halothane
Vessle-rich group	32 ± 10	27 ± 9	30 ± 8	12 ± 2*	10 ± 3	8 ± 2
Muscle group	5.7 ± 1.6	5.1 ± 1.5	5.7 ± 1.0	17 ± 3	14 ± 5	9 ± 2†
Fourth compartment	11 ± 3	11 ± 3	11 ± 2	6 ± 3‡	5 ± 2‡	3 ± 1‡
Fat group	2.1 ± 0.4	2.2 ± 0.2	2.1 ± 0.4	5 ± 3	6 ± 3	4 ± 2

Values are mean ± SD.
* Significantly different from isoflurane and halothane ($P < 0.05$).
† Significantly different from desflurane and isoflurane ($P < 0.05$).
‡ Significantly different from the other anesthetics ($P < 0.05$).

TABLE 6. Pulmonary Recovery of Anesthetics

Anesthetic	Total Uptake (ml)	Pulmonary Elimination (ml)	Anesthetic Recovered (%)	Normalized Recovery* (%)
Desflurane	411 ± 61	421 ± 65	105 ± 25	102 ± 14
Isoflurane	155 ± 46	158 ± 48	102 ± 13	100
Halothane	112 ± 12	72 ± 13	64 ± 9†	63 ± 6†

Values are mean ± SD.
* Normalized to the recovery of isoflurane.
† Significantly different from desflurane and isoflurane ($P < 0.05$).

analysis in this and similar studies we have performed reasonably approximate those obtained by mammillary analysis. This is particularly true of the terminal constant but also applies to the other constants, with the possible exception of the time constant for the first compartment, for which the mammillary values are approximately twice the hybrid values. There is an obvious, very high correlation between the hybrid and mammillary results across compartments (*i.e.*, regressing results for all compartments). More impressive yet is that regressions for intracompartment analyses, except for the lung group, are good: for the FG the r^2 value is 0.86; for the fourth compartment, 0.72; for the MG, 0.29; and for the VRG, 0.37 (all correlations with $P < 0.002$). Such data suggest that the hybrid results might substitute for the mammillary results, particularly for the FG and the fourth compartments.

However, the accuracy of the hybrid time constants depends on a substantial separation of compartment characteristics. For the current data those separations are considerable. Each time constant is approximately one order of magnitude greater than the preceding time constant. Where such separation is not achieved, accuracy suffers and the hybrid values may not accurately approximate the mammillary values. Of course, under these circumstances it also may be difficult or impossible to determine the mammillary values.

The capacity to predict time constants and tissue volumes from the kinetic data in many respects is limited. Although the estimates of FG blood flow from the mammillary values are consistent with those obtained with other techniques,[32] the estimates of blood flow for the VRG are smaller and for the MG are greater than those obtained by more invasive but more accurate techniques. For desflurane, the total tissue volumes approximate the known total body volume (the total is about 40 l, which, we assume, does not include essentially avascular tissues such as cartilage), but the estimates from the data for isoflurane and halothane provide an appreciable underestimate. The data for tissue blood flows are consistent among anesthetics. However, tissue volumes for halothane tend to be smaller than the volumes for isoflurane, and those for isoflurane tend to be smaller than those for desflurane.

Indeed, the discrepancy between the predicted and observed values for time constants and tissue volumes (and for the latter, the variability among anesthetics) calls into question the adequacy of: 1) the data; 2) the kinetic analysis; and/or 3) the paradigm currently used to explain pharmacokinetics in physiologic terms. The data may be suspect in that there is an underlying assumption that the FA accurately indicates the anesthetic partial pressures in arterial blood. Although there appears to be a good correlation between the two, gradients exist.[33,34] These will be larger during periods of considerable change in concentration (*i.e.*, during the periods of initial administration and elimination) and thus may confound our ability to accurately predict volumes and time constants for the lungs and the VRG. Since the estimates for V_1 also depend to a great extent on the measurements made during this time, V_1 also may be assessed inaccurately, thereby contributing to erroneous estimates, particularly of tissue volumes. The period after anesthesia, when subjects did not remain at a basal state (with consequent changes in ventilation, cardiac output, and distribution of blood flow) also may contribute to discontinuities in the data and hence "errors" in the kinetic analysis. However, this should most affect values for fat, and our calculated values for blood flow appear to accurately reflect known values.

Our paradigm of the pharmacokinetics of inhaled anesthetics is based in part on known data for tissue volumes and blood flows. Anesthetic diffusion, however, may distort the effect of volumes and flows. For tissues with limited blood flow (*e.g.*, muscle), the presumed equilibration may be incomplete. For adjacent tissues with widely different time constants, intertissue diffusion may occur—as postulated to explain the existence of the fourth compartment. We may not have accounted for all such intertissue diffusions (*e.g.*, lung to adjacent intercostal muscle; intestine to the parietal peritoneum and adjacent muscle; kidney to the psoas muscle) or for countercurrent diffusion between arterial and venous anesthetic partial pressures.

The pulmonary clearances did not differ among anesthetics despite the differences in solubilities (a threefold difference). Although k_{10} was, as might be anticipated, inversely correlated with solubility, the opposite change in V_1 resulted in the absence of a difference. Total

body clearance of desflurane and halothane exceeded that of isoflurane. This result may be predicted from the differences in solubility and biodegradation of these compounds. The low solubility of desflurane would increase its clearance; the biodegradation of halothane would increase its clearance.

In summary, our results indicate that recovery from anesthesia with desflurane in humans will be more rapid than recovery with currently used volatile anesthetics. Our results also indicate that desflurane resists biodegradation by humans and thus may have little or no toxic potential.

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References

1. Eger EI II: Partition coefficients of desflurane in human blood, saline, and olive oil. Anesth Analg 66:971–973, 1987
2. Yasuda N, Targ AG, Eger EI II: Solubility of desflurane, sevoflurane, isoflurane, and halothane in human tissues. Anesth Analg 69:370–374, 1989
3. Jones RM, Cashman JN, Eger EI II, Damask MC, Johnson BH: Kinetics and potency of desflurane (I-653) in volunteers. Anesth Analg 70:3–7, 1990
4. Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB: Pharmacokinetics of inhaled anesthetics in humans: Measurements during and after simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane, and nitrous oxide. Anesth Analg 65:575–582, 1986
5. Koblin DD, Eger EI II, Johnson BH, Konopka K, Waskell L: Desflurane resists degradation in rats. Anesth Analg 67:534–538, 1988
6. Koblin DD, Weiskopf RB, Holmes MA, Konopka K, Rampil IJ, Eger EI II, Waskell L: Metabolism of desflurane and isoflurane in swine. Anesth Analg 68:147–149, 1989
7. Yasuda N, Eger EI II, Targ AG, Weiskopf RB, Johnson BH: The pharmacokinetics of desflurane, sevoflurane, isoflurane and halothane in pigs. Anesth Analg 71:340–348, 1990
8. Holaday DA, Smith FR: Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. ANESTHESIOLOGY 54:100–106, 1981
9. Siebeck R: Uber die aufnahme von stickoxydul in blut. Skand Arch Physiol 21:368–382, 1909
10. Glantz SA: Primer of Biostatistics. New York, McGraw-Hill, 1981, pp 87–88
11. Jennrich R: Nonlinear regression, BMDP Statistical Software. Edited by Dixon WJ. Berkeley, University of California Press, 1983, pp 290–304
12. Ralston M: Derivative-free nonlinear regression, BMDP Statistical Software. Edited by Dixon WJ. Berkeley, University of California Press, 1983, pp 305–314
13. Boxenbaum HG, Riegelman S, Elashoff RM: Statistical estimations in pharmacokinetics. J Pharmacokinet Biopharm 2:123–148, 1974
14. Zar JH: Biostatistical Analysis. Englewood Cliffs, Prentice-Hall, 1984, pp 153–155
15. Lockhart SH, Eger EI II: Absence of abundant saturable binding sites for halothane or isoflurane in rabbit brain: Inhaled anesthetics obey Henry's Law. Anesth Analg 71:70–72, 1990
16. Coburn CM, Eger EI II: The partial pressure of isoflurane or halothane does not affect their solubility in rabbit blood or brain or human brain: Inhaled anesthetics obey Henry's Law. Anesth Analg 65:960–962, 1986
17. Rowland M, Benet LZ, Graham GG: Clearance concepts in pharmacokinetics. J Pharmacokinet Biopharm 1:123–136 1973
18. Zar JH: Biostatistical Analysis. Englewood Cliffs, Prentice-Hall, 1984, pp 219–222
19. Eger EI II: The effect of inspired anesthetic concentration on the rate of rise of alveolar concentration. ANESTHESIOLOGY 24: 153–157, 1963
20. Eger EI II, Smith RA, Koblin DD: The concentration effect can be mimicked by a decrease in blood solubility. ANESTHESIOLOGY 49:282–284, 1978
21. Eger EI II, Johnson BH: Rates of awakening from anesthesia with desflurane, halothane, isoflurane, and sevoflurane: A test of the effect of anesthetic concentration and duration in rats. Anesth Analg 66:977–982, 1987
22. Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB: Does the duration of anesthetic administration affect the pharmacokinetics or metabolism of inhaled anesthetics in humans? Anesth Analg 65:575–582, 1986
23. Rehder K, Forbes J, Alter H, Hessler O, Steir A: Halothane biotransformation in man: A quantitative study. ANESTHESIOLOGY 28:711–715, 1967
24. Holaday DA, Fiserova-Bergerova V, Latto IP, Zumbiel MA: Resistance of isoflurane to biotransformation in man. ANESTHESIOLOGY 43:325–332, 1975
25. Munson ES, Eger EI II, Tham MK, Embro WJ: Increase in anesthetic uptake, excretion and blood solubility in man after eating. Anesth Analg 57:224–231, 1974
26. Frumin MJ, Salanitre E, Rackow H: Excretion of nitrous oxide in anesthetized man. J Appl Physiol 16:720–722, 1961
27. Salanitre E, Rackow H, Greene LT, Klonymus D, Epstein RM: Uptake and excretion of subanesthetic concentrations of nitrous oxide in man. ANESTHESIOLOGY 23:814–822, 1962
28. Sheffer L, Steffenson JL, Birch AA: Nitrous oxide-induced diffusion hypoxia in patients breathing spontaneously. ANESTHESIOLOGY 37:436–439, 1972
29. Eger EI II, Larson CP: Anaesthetic solubility in blood and tissues: Values and significance. Br J Anaesth 36:140–149, 1964
30. Assali NS, Ross M: Nitrous oxide solubility in fetal and uterine tissues in human pregnancy. Proc Soc Exp Biol 100:497–498, 1959
31. Steward A, Allot PR, Cowles AL, Mapleson WW: Solubility coefficients for inhaled anaesthetics for water, oil and biological media. Br J Anaesth 45:282–293, 1973
32. Eger EI II: Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974, p 88
33. Eger EI II, Babad AA, Regan MH, Larson CP, Jr, Shargel R, Severinghaus JW: Delayed approach of arterial to alveolar nitrous oxide partial pressure in dog and man. ANESTHESIOLOGY 27:288–297, 1966
34. Carpenter RL, Eger EI II: Alveolar-to-arterial-to-venous anesthetic partial pressure differences in humans. ANESTHESIOLOGY 70: 630–635, 1989