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Recovery and Kinetic Characteristics of Desflurane and Sevoflurane in Volunteers after 8-h Exposure, including Kinetics of Degradation Products

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***Background*: Desflurane and sevoflurane permit speedier changes in anesthetic partial pressures than do older halogenated anesthetics. The authors determined the kinetic characteristics of desflurane and sevoflurane and those of compound A [CH_2F-O-C(=CF_2)(CF_3)], a nephrotoxic degradation product of sevoflurane.**

***Methods*: Volunteers received 1.25 minimum alveolar concentration of desflurane or sevoflurane, each administered for 8 h in a fresh gas inflow of 2 l/min. Inspired (F_I) and end-tidal (F_A) concentrations of anesthetic and compound A were measured during administration, and F_A relative to F_{A0} (the last end-tidal concentration during administration) during elimination. The indices of recovery were also measured.**

***Results*: The ratio F_I/F_A rapidly approached 1.0, with values greater for sevoflurane (desflurane 1.06 ± 0.01 *vs.* sevoflurane 1.11 ± 0.02, mean ± SD). The ratio F_A/F_I for compound A was approximately 0.8. The F_A/F_{A0} ratio decreased slightly more rapidly with desflurane than with sevoflurane, and objective measures indicated faster recovery with desflurane: The initial response to command (14 ± 4 min *vs.* 28 ± 8 min [means ± SD]) and orientation (19 ± 4 *vs.* 33 ± 9 min) was quicker, and recovery was faster as defined by results of the Digit Symbol Substitution, P-deletion, and Trieger tests. Desflurane produced less vomiting (1 [0.5, 3]; median [quartiles] episodes) than did sevoflurane (5 [2.5, 7.5] episodes). The F_A/F_{A0} ratio for compound A decreased within 5 min to a constant value of 0.1.**

***Conclusions*: These anesthetics have kinetics consistent with their solubilities. Sevoflurane's greater biodegradation probably increases F_I/F_A differences during anesthetic administration and decreases F_A/F_{A0} differences during elimination. The F_A for compound A differs from F_I by 20% (F_A/F_I = 0.8) because of substantial degradation. Recovery from anesthesia proceeds nearly twice as fast with desflurane than with sevoflurane. Differences in ventilation, or alveolar or tissue elimination, do not completely explain the slower recovery with sevoflurane. (Key words: Anesthetics, volatile: desflurane; sevoflurane; compound A; kinetics. Anesthetics, volatile: desflurane; sevoflurane; compound A; recovery.)**

SEVOFLURANE and desflurane were developed to address the perception that a less soluble anesthetic would better serve the needs of today's anesthesia practitioner. The kinetic advantages of each agent have been demonstrated relative to older anesthetics, such as isoflurane,[1,2] and more rapid immediate and longer-term recovery follows anesthesia with desflurane or sevoflurane.[3–6] Consistent with the lower solubility of desflurane in blood and tissues,[7–9] studies in rats indicate that recovery after anesthesia with desflurane is approximately twice as fast as recovery after anesthesia of equivalent depth and duration with sevoflurane.[10] Two studies in patients also suggest a more rapid initial recovery after desflurane is used.[11,12] These studies of brief anesthesias found no difference in the quality of awakening, except for a greater incidence of excitation in children recovering from anesthesia with desflurane.[11] Neither study tested the comparative effects of prolonged anesthesia.

Two limitations apply to the kinetic data available for desflurane and sevoflurane.[1,2] First, measures of uptake were obtained during delivery of a constant inspired concentration (F_I), but normal clinical practice is to adjust the F_I to achieve a desired end-tidal concentration (F_A). Second, the kinetics of compound A (which are

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linked to the administration of sevoflurane) have not been adequately defined during either administration or elimination of sevoflurane. We hypothesized that compound A kinetics may differ markedly from those of other inhaled compounds because it undergoes rapid degradation in the protein components of blood,[13] and probably lean tissues as well.

We supply data for volunteers given 8 h of anesthesia at 1.25 minimum alveolar concentration (MAC) of each anesthetic at the lowest inflow rate (2 l/min) recommended for sevoflurane by the US Food and Drug Administration. Specifically, we provide data for the kinetics of desflurane, sevoflurane, and compound A and for the recovery characteristics of desflurane *versus* sevoflurane. The data were obtained from volunteers also studied for the comparative toxicity of sevoflurane (and compound A) *versus* desflurane.[14]

Materials and Methods

Study Population

With approval from the University of California Committee on Human Research and patients' informed consent, we studied 12 healthy male volunteers. The original protocol proposed an open-label study in which each volunteer would be anesthetized twice, with a 14-day interval between studies. One half of the participants were to receive sevoflurane first, and the other half desflurane, with the alternate anesthetic given second. Because several volunteers preferred not to receive a second anesthetic, only seven men received both anesthetics; three received only sevoflurane and two only desflurane. Entry criteria included normal results of medical history and physical examination and negative laboratory results, including urinary tests for illicit drugs.

Experimental Design

One or more days before the day of the study, the volunteers completed the Digit Symbol Substitution (DSST), P-deletion, and Trieger tests, as used by previous investigators.[4,6] The DSST requires the volunteer to assign appropriate symbols to a table of digits from a separate table that identifies each digit by a symbol (*e.g.*, a circle or a cross). The volunteer was given 90 s to make as many assignments as possible. The score for the DSST equals the sum of the number of correct symbol substitutions. The connection between number and symbol in subsequent DSST tests was altered so that for a given volunteer, no two tests were the same. The P-deletion test (a 3-min test in which the participant uses a pen to cross out as many as possible of a hundred randomly placed P's embedded in a page of random letters) is scored as the number of P's correctly deleted. The Trieger test requires that the volunteer draw a line through a pattern of dots on a single page. The volunteer is encouraged with each test to draw the line through each dot. The Trieger test is scored as the sum of the minimum distances (measured in millimeters) that the drawn line deviated from each dot. Neither the array of P's in the P-deletion test nor the pattern used for the Trieger test were varied in sequential tests.

On the day of the study, we placed an intravenous cannula in each volunteer and applied standard clinical monitors. After preoxygenation for at least 3 min and infusion of 100 mg lidocaine, we induced anesthesia with propofol (2 mg/kg). Administration of vecuronium (0.1 mg/kg) facilitated tracheal intubation with a 7-mm cuffed tube. We connected an "artificial nose" (HumidVent 1; Gibeck Respiration, AB, Väsby, Sweden) to the tracheal tube for airway humidification. Inspiratory and end-tidal gas samples were drawn into 50-ml glass syringes stored with the plunger upright (to ensure a small positive pressure in the syringe) until the gas samples were analyzed. Inspired samples were taken manually from the inspiratory limb of the circuit, and end-tidal samples were taken from the endotracheal tube at a point just distal to the artificial nose. Insertion of an 80-ml dead space between the circle Y-piece and the artificial nose prevented inspired gas from contaminating the end-tidal samples.

Volunteers received desflurane or sevoflurane from a standard anesthetic machine and circle absorber circuit (Ohmeda 8000 with respective Tec-6 and Tec-5 vaporizers; Ohmeda, Madison, WI). To provide standard and consistent absorbent conditions, both absorbent canisters were filled with fresh absorbent (Sodalime: Puritan-Bennett, Lenexa, KS—eight participants; or Baralyme Brand Absorbent: Chemetron, St. Louis, MO—four volunteers; the same absorbent being used for both anesthetics in a given volunteer) before each study. The temperature at the center of the absorbent layer 1–2 cm from the bottom of the lower canister (*i.e.*, the layer from which gases exit the canister) was measured and recorded at 15-min intervals.

By manipulating vaporizer settings, we produced a stable end-tidal concentration of 1.25 MAC (for the age group studied, MAC equals 7.25% desflurane or 2.4% sevoflurane in oxygen,[15,16] giving sustained concentra-

tions of 9% and 3%, respectively) within 5–10 min after anesthesia was induced with propofol. We first delivered 6 l/min inflow rates and then lowered the inflow to 2 l/min, where it was kept for 8 h. We used 1 l/min of air and 1 l/min of oxygen, producing an $F_{I_{O_2}}$ of 0.45–0.5. We used displacement spirometry to calibrate the flowmeters. Breath-by-breath anesthetic and carbon dioxide concentrations were measured using an Ultima infrared analyzer (Datex Corp., Helsinki, Finland) calibrated with secondary cylinder calibration gases. External application of warm air (Bair-Hugger; Augustine Medical, Eden Prairie, MN) maintained esophageal temperature at 37°C. We instituted mechanical ventilation at 10–13 breaths/min, with a tidal volume that produced an end-tidal concentration of carbon dioxide of 28–32 mmHg. Lactated Ringer's solution was infused at 1–3 ml · kg^{-1} · h^{-1}, a rate sufficient to supply approximately 3 l/day (*i.e.*, a normal replacement in the absence of fluid losses such as those produced by surgical trauma). Blood pressure was maintained at a mean value of 50 mmHg or higher by adjusting the volunteer's position, increasing the infusion of lactated Ringer's solution, or both. No vasopressor was given to any volunteer. Each participant lay on a padded table, and extremities were flexed and the head repositioned each hour.

At 1, 5, 10, 15, 20, 30, 60, 120, 180, 240, 300, 360, 420, and 480 min, inspired and end-tidal samples of gas were obtained and analyzed for sevoflurane and compound A, or for desflurane, using gas chromatography. During administration of sevoflurane, we also measured the concentrations of hexafluoroisopropanol and n-pentane in end-tidal gases, using gas chromatography. We also measured the concentration of n-pentane in volunteers given desflurane.

After 8 h of 1.25 MAC anesthesia, the fresh gas inflow was changed to 2 l/min of oxygen, and spontaneous ventilation was achieved by providing hypoventilation (with the tracheal tube still in place). The end-tidal vapor concentration was not changed. We gave 30 mg of propofol, aspirated secretions from the throat, and removed the tracheal tube. Anesthesia at 1.25 MAC was continued *via* mask until spontaneous ventilation resumed (in approximately 5 min). Anesthetic administration was discontinued, and a non-rebreathing system was applied *via* face mask. The inspired oxygen was maintained at approximately 40% by adding oxygen. End-tidal gases were sampled and analyzed by gas chromatography for anesthetic gas concentrations and concentrations of compound A at 1, 3, 5, 10, 15, 20, 30, 45, and 60 min during spontaneous ventilation. We also recorded infrared values for anesthetic at these times in all but one volunteer in each anesthetic group. In 8 of 11 volunteers recovering from anesthesia with sevoflurane and in 6 of 9 volunteers recovering from anesthesia with desflurane, we obtained one or more measurements of minute ventilation at the times when samples were drawn for analysis by gas chromatography.

During anesthetic elimination, each volunteer was asked at 1-min intervals to open his eyes and to squeeze the investigator's hand. The time to an appropriate response was noted. At 2-min intervals after appropriate response, the volunteer was asked to identify place and date. These questions were repeated until correct answers were given. As wakefulness permitted, we obtained results for the DSST, P-deletion test, Trieger test, and Aldrete Recovery score at 15, 30, 45, 60, 75, and 90 min after cessation of anesthetic administration. At the same time points, using a visual analog scale ranging from 0 (worst) to 10 (best), we asked each man to evaluate his sense of clear-headedness and his sense of energy. Concurrently, we asked each volunteer to assess his degree of nausea using a visual analog scale ranging from 0 (no nausea) to 10 (severe nausea). Control values for all visual analog scales were obtained before anesthesia.

All volunteers remained in the study area for 4 h after discontinuation of anesthetic administration (the recovery period) and were then discharged, accompanied home by a responsible person. The number of emetic episodes during this 4-h period was recorded. An episode was defined as one or more contiguous vomits of gastric contents. All episodes were separated by several minutes. The observers of emetic episodes were not blinded to the anesthetic administered.

At least 1 week after administration of the second anesthetic, each volunteer given both anesthetics (n = 7) was asked to complete a questionnaire to estimate times to complete recovery of various end points, including time to complete recovery: (1) all normal functions, (2) the capacity to focus the eyes, (3) the capacity to concentrate, (4) normal mental function, (5) from nausea, (6) to normal balance, (7) from a sore throat and muscle or joint aches.

Data Analysis

Data for anesthetic and compound A kinetics were summarized as the approach of the inspired concentration (F_I) to the alveolar concentration (F_A) during anes-

thetic administration (*i.e.*, F_I/F_A was the inverse of the usual F_A/F_I; F_I/F_A was chosen because F_A rather than F_I was held constant), and as the rate of decay of the alveolar concentration during elimination of anesthetic relative to the last alveolar concentration during administration of anesthetic (F_{A0}) (*i.e.*, F_A/F_{A0}). Using the trapezoid rule, we averaged the area under the curve for F_I/F_A and F_A/F_{A0} for desflurane *versus* sevoflurane, except that we did not include the values for the 1- and 3-min measurements of F_A/F_{A0} because ventilation was too unstable during this time to yield accurate measurements. For each volunteer we calculated the area under the curve for F_I/F_A and F_A/F_{A0} and compared these averages between anesthetic groups with a *t* test, accepting probability values < 0.05 as significant.

Measures of time of return to consciousness (time from discontinuation of anesthetic administration to appropriate response to command and appropriate naming of place and date) were compared between anesthetics by paired and unpaired *t* tests. We accepted probability values < 0.05 as significant.

Only two volunteers, both given desflurane, recovered rapidly enough to complete the more complex measures of mental function at 15 min, and only three or four men given sevoflurane recovered rapidly enough to complete these measures through 45 min. At 30 min and later with desflurane, and at 60 min or later with sevoflurane, all or all but one volunteer could complete these measures. Accordingly, no scores for desflurane were entered for the first 15 min after anesthesia, and no scores for sevoflurane were entered for the first 45 min after anesthesia. Values for a given volunteer were analyzed as the fraction of the value before anesthesia (*i.e.*, the control value). The averages at each time point were compared by a paired or unpaired *t* test. Because we made three comparisons (data for time points 60, 75, and 90 min after anesthesia), we accepted probability values < 0.015 as significant (with Bonferroni correction).

For the Trieger test, we obtained the value for the sum of the minimum distances (in millimeters) of the line from each dot. No score was entered if the volunteer did not complete the test. Because the data were skewed, scores between anesthetics were compared using the nonparametric Mann-Whitney U test. As with the DSST and P-deletion tests, fewer than one half the volunteers given sevoflurane could complete the Trieger test before 60 min after anesthesia. Thus only three comparisons were made among subjects given desflurane and those given sevoflurane, and we accepted probability values < 0.015 as significant.

Variables measured using visual analog scales (clear headedness, sense of energy, nausea) were compared for values obtained at 60, 75, and 90 min after anesthesia between anesthetic groups using a Mann-Whitney U test. We accepted probability values < 0.015 as significant.

Because they were *post hoc* measurements, we did not perform any statistical comparisons of the subjective paired subjects' estimates of time to complete recovery of various functions. Statistical analysis also would be compromised by the interrelated rather than independent (*i.e.*, a change in one may influence a change in another) nature of these data.

The number of episodes of emesis was compared using a binomial distribution test. For this comparison, we accepted probability values < 0.05 as significant.

Gas Chromatographic Analyses

For analysis of anesthetic and compound A concentrations, we used a flame ionization detector gas chromatograph (Gow-Mac 580, Bethlehem, PA) equipped with a 1-m long, 2.2-mm internal diameter column containing Porapak Q (Alltech Associates, Inc., Deerfield, IL) maintained at 125°C with a 10-ml/min carrier flow of nitrogen. The detector (at 175°C) received hydrogen at 55 ml/min and air at 200 ml/min. The chromatograph was calibrated before and at intervals during each test using secondary (cylinder) calibration standards. We prepared primary (volumetric) standards to calibrate each secondary standard.

To analyze hexafluoroisopropanol and n-pentane concentrations, we used a flame ionization detector gas chromatograph (Gow-Mac 750) equipped with a 12-m long, 2.2-mm internal diameter column containing SF-96 maintained at 100°C with a 10 ml/min carrier flow of nitrogen. The detector (at 200°C) received hydrogen at 40 ml/min and air at 300 ml/min. The chromatograph was calibrated before and at intervals during each test using secondary (cylinder) calibration standards. We prepared primary (volumetric) standards to calibrate each secondary standard.

Materials

Sevoflurane was purchased from Abbott Laboratories (North Chicago, IL). Desflurane and compound A (used to establish standards) were given to us by Ohmeda, Pharmaceutical Products Div. (Liberty Corner, NJ).

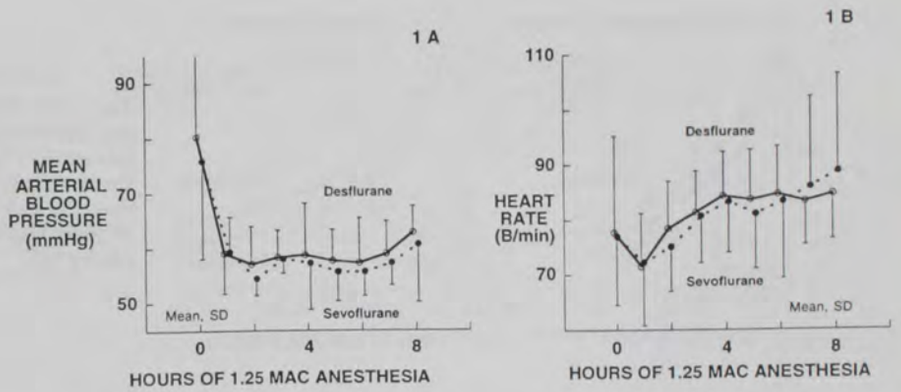

Fig. 1. Neither mean arterial blood pressure (*A*) nor heart rate (*B*) differed significantly between volunteers given desflurane and those given sevoflurane.

Results

Physical Comparisons, Vital Signs, and End-tidal Anesthetic Concentrations

As reported in the sister study of these volunteers,[14] demographic, ventilatory, and cardiovascular data did not differ among volunteers given desflurane and those given sevoflurane. Vital signs did not differ between anesthetic groups at any time during anesthesia or thereafter (fig. 1; lowest $P = 0.29$). During anesthesia and immediate recovery, volunteers given desflurane received 1,200 ± 300 ml lactated Ringer's solution, whereas those given sevoflurane received 1,500 ± 400 ml ($P = 0.06$).

With resumption of spontaneous ventilation *via* a mask, end-tidal carbon dioxide increased to values between 50–60 mmHg, decreasing thereafter to values usually between 40–50 mmHg with elimination of the anesthetic. Similarly, minute ventilation increased with elimination of the anesthetic (fig. 2). There was no systematic difference in carbon dioxide or minute ventilation values between the two anesthetic groups.

Kinetic Studies of Anesthetics

Consistent with the infrared analysis, gas chromatography confirmed achievement of the target end-tidal anesthetic concentrations (*i.e.*, 9.0 ± 0.2% desflurane and 3 ± 0% sevoflurane). We found no differences for gas chromatographic *versus* infrared analysis. The inspired concentrations of both anesthetics rapidly approached, but did not reach, the concentration maintained in the alveoli (*i.e.*, the F_I/F_A ratio approached 1.0), with desflurane coming closer at any given time point (fig. 3). The area under the curve for the F_I/F_A ratio of 1.07 ± 0.01 for sevoflurane exceeded the 1.04

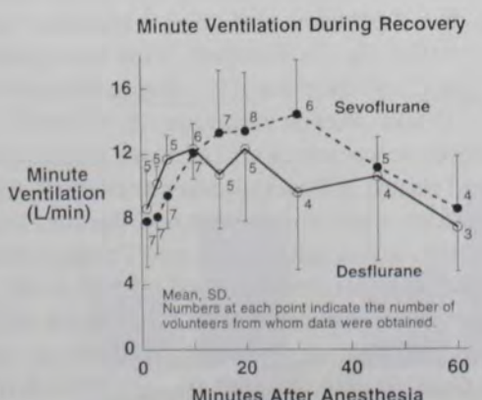

Fig. 2. Minute ventilation increased with elimination of either anesthetic, reaching a peak 15 to 30 min after anesthesia. No consistent difference was found between the anesthetic groups. Values are given as means ±SD. The numbers for each point are the numbers of participants for whom a measurement of ventilation was obtained.

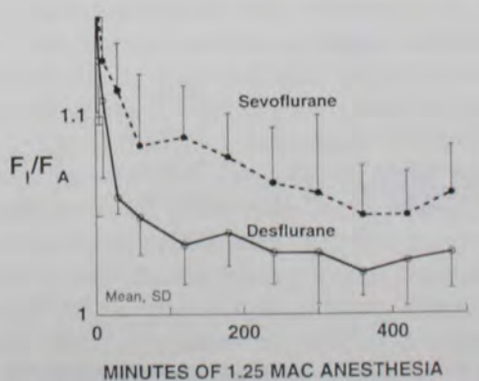

Fig. 3. The F_I/F_A ratios for both desflurane and sevoflurane approached, but did not reach, 1.0. The difference from 1.0 was approximately half as great for desflurane as for sevoflurane. The average F_I/F_A ratio was significantly higher for sevoflurane.

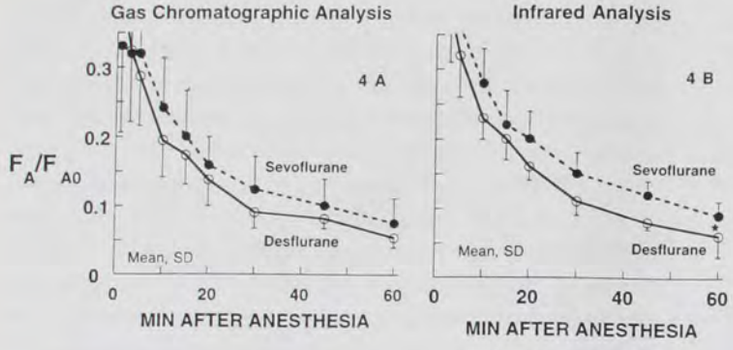

Fig. 4. The F_A/F_{A0} ratios for both desflurane and sevoflurane decreased rapidly after cessation of anesthetic administration. The average value for the desflurane F_A/F_{A0} ratios was less than that for sevoflurane. For both anesthetics, the values obtained using infrared analysis (*B*) were slightly higher than those obtained using gas chromatography (*A*).

$\pm$ 0.01 value for desflurane ($P < 0.0001$). Elimination of both anesthetics (F_A/F_{A0} ratio) was rapid. The average F_A/F_{A0} ratio of 0.130 $\pm$ 0.031 for sevoflurane exceeded the 0.104 $\pm$ 0.018 value for desflurane for the gas chromatographic data at 5 min and later ($P < 0.003$; fig. 4A). An exponential fit to the data for 5–60 min yielded the following equations: desflurane: $Y = 0.259 \cdot e^{-0.0285X}$; sevoflurane: $Y = 0.283 \cdot e^{-0.0246X}$, where Y is the F_A/F_{A0} ratio and X is time expressed in minutes. Respective chi-square values were 0.71 and 0.64. We found slightly higher values for F_A/F_{A0} for each anesthetic using infrared analysis (fig. 4B). Ventilation during anesthetic elimination did not differ between anesthetics except at 30 min, when it was greater with sevoflurane than with desflurane. We found no measurable levels of hexafluoroisopropanol or n-pentane (limit of detection, 0.1–1.0 ppm) at any evaluation time point.

Kinetic Studies of Compound A

F_A/F_I for compound A rapidly increased to a relatively constant value of 0.8 after 1–2 h (fig. 5). This increase paralleled the increase in temperature in the lower layer of absorbent. Elimination of compound A followed an unusual course (fig. 6B), one that differed from that seen with sevoflurane (fig. 6A). The F_A for compound A decreased rapidly to a constant low value of approximately 10% (*i.e.*, slightly less than 3 ppm) of the value at the end of anesthesia (F_{A0}), whereas an exponential decline was found with sevoflurane and desflurane (figs. 4 and 6). The choice of absorbent did not affect the concentrations of compound A obtained: the average inspired and end-tidal concentrations were 40.1 $\pm$ 3.4 ppm and 31.2 $\pm$ 3.0 ppm, respectively, with soda lime (n = 6), and 42.6 $\pm$ 3.3 ppm and 32.5 $\pm$ 3.3 ppm with Baralyme (n = 4). These values for all volunteers (n = 10) were 41.1 $\pm$ 3.4 ppm and 31.7 $\pm$ 3.0 ppm, respectively.

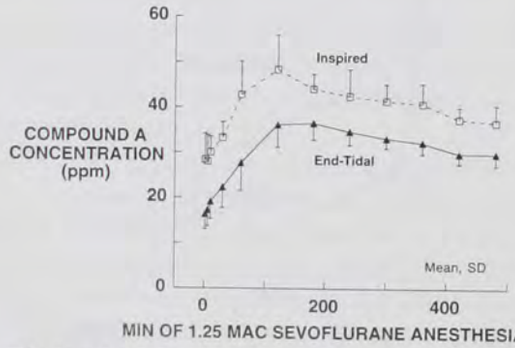

Fig. 5. The inspired (F_I) concentration of compound A peaked 2 h after initiating administration of 1.25 MAC (3%) sevoflurane. The end-tidal (F_A) concentration of compound A paralleled F_I, and after 2 h, the value for F_A/F_I equaled approximately 0.8.

Indices of Recovery

Awakening occurred more rapidly after desflurane anesthesia. Time to initial response to command was 14 $\pm$ 4 min after desflurane and 28 $\pm$ 8 min after sevoflurane ($P < 0.001$; fig. 7). Similarly, time to correct statement of place and date was 19 $\pm$ 4 min after desflurane and 33 $\pm$ 9 min after sevoflurane ($P < 0.001$; fig. 7). Other objective measures of recovery also indicated a more rapid return of function after anesthesia with desflurane than after anesthesia with sevoflurane. The DSST and P-deletion test results (fig. 8) and Trieger test results (data not shown) returned toward normal more rapidly after anesthesia with desflurane. The mean values for desflurane differed significantly from those for sevoflurane from 60 min through 90 min ($P < 0.015$, except for the P-deletion test at 90 min where $P < 0.1$). Aldrete recovery scores initially were lower for sevoflurane, equaling those for desflurane at 1 h after cessation of anesthetic administration.

During the 90 min immediately after cessation of anes-

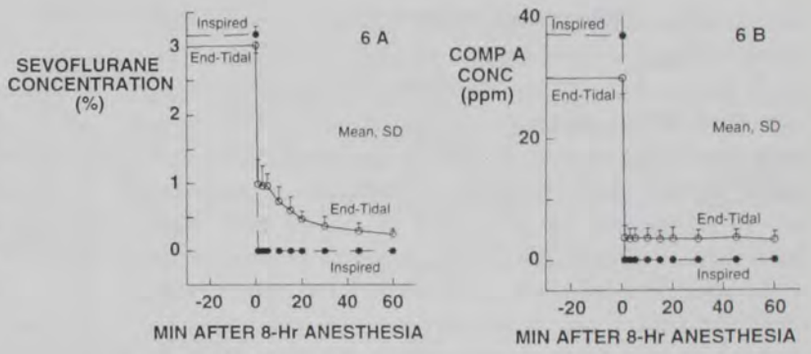

Fig. 6. With cessation of administration of sevoflurane and conversion to a nonrebreathing system, the inspired concentration of sevoflurane (*A*) and compound A (*B*) decreased immediately to zero. The end-tidal concentrations also decreased rapidly. For sevoflurane, the decrease followed the expected exponential decay, but did not for compound A. Instead, the compound A concentration decreased to a constant level, equaling approximately 10% of the value at the end of sevoflurane administration.

thetic administration, the subjective measure, sense of clear headedness, was significantly greater ($P < 0.01$ for all points of comparison after 30 min) after desflurane anesthesia than after sevoflurane anesthesia. Although the subjective measures of nausea and sense of energy did not differ significantly for the two anesthetics, emetic episodes occurred more frequently in the 4 h of recovery after sevoflurane anesthesia. For the seven volunteers given both anesthetics, all but one vomited more times after sevoflurane than after desflurane anesthesia (one volunteer did not vomit after either anesthetic). There were five (2.5, 7.5; median [quartiles]) emetic episodes after sevoflurane anesthesia and one (0.5, 3) episode after desflurane anesthesia ($P = 0.03$).

Finally, volunteers given desflurane appeared to return to complete normality (mental and physical) more rapidly than did volunteers given sevoflurane. For example, the men in the sevoflurane group reported that they "felt normal in all respects" 72 (72, 84) h (median [quartiles]) after anesthesia, whereas the men in the desflurane group took 12 h (9, 27) to reach the same end point. Similarly, nausea was gone 24 h (7, 30) after sevoflurane anesthesia and 4 h (3, 5) after desflurane anesthesia; muscle coordination returned to normal 24 h (11, 84) *versus* 6 h (3, 10); and the ability to concentrate became normal at 36 h (9, 54) *versus* 4 h (4, 9). We did not analyze these subjective *post hoc* interrelated data further.

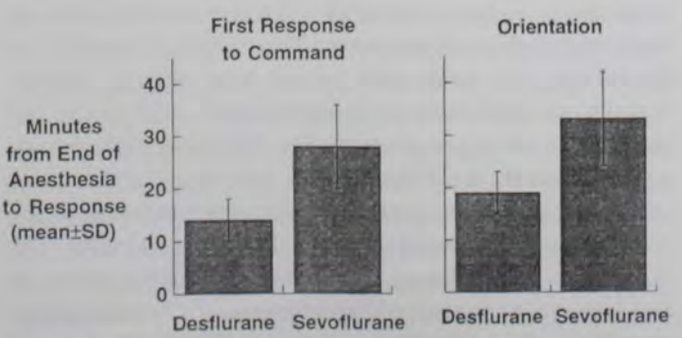

Fig. 7. The time (in minutes) to response to command ("open your eyes; squeeze my hand") and to orientation to place and date ("Where are you? What day is it?") was half as long after 8 h of 1.25 MAC anesthesia with desflurane than after 8 h of 1.25 MAC anesthesia with sevoflurane. Values are given as the mean ± SD.

Discussion

The more rapid approach of the inspired to end-tidal concentrations with desflurane than sevoflurane (fig. 3) during anesthetic administration is consistent with the lower solubilities of desflurane in blood, lean tissues, and fat,[7-9] and it qualitatively confirms earlier study results for far shorter durations of anesthesia.[1,2] Similarly, when viewed as a group of paired data, F_A/F_{A0} (elimination) values differed for the data obtained using either gas chromatography or infrared analysis (fig. 4).

We propose that the difference between F_I/F_A for sevoflurane and that for desflurane during anesthetic administration (fig. 3) is greater than might be explained by their differences in solubility, and that the difference for F_A/F_{A0} (fig. 4) is smaller than might be explained by differences in solubility. We believe these deviations from solubility-based predictions result from the added effect of anesthetic metabolism, an effect that enhances the uptake of sevoflurane during its administration and accelerates the decline of F_A/F_{A0} during elimination of anesthetic. Such deviations have been described previously for halothane and methoxyflurane.[1,17,18] Metabolism of sevoflurane is more than 100 times greater than that of desflurane; approximately 0.02% of desflurane taken up can be recovered as metabolites (primarily trifluoroethanol), whereas 3–5% of sevoflurane taken

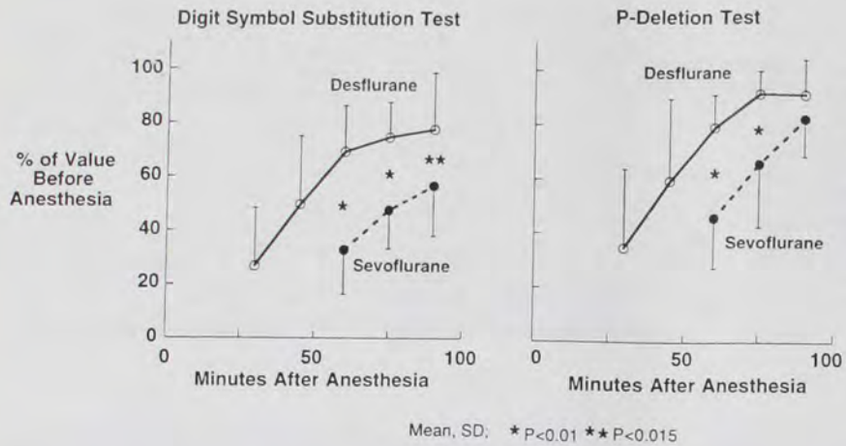

Fig. 8. The return to control values for the Digit Symbol Substitution test and P-deletion test occurred more rapidly after anesthesia with desflurane than after anesthesia with sevoflurane. The values for 60 and 75 min differed significantly ($P < 0.01$), and the values at 90 min tended to significance (P-deletion, $P = 0.1$) or reached significance (Digit Symbol Substitution test, $P < 0.015$). Note that data points are missing (and no statistical comparisons are made) for 15 min for desflurane and for 15, 30, and 45 min for sevoflurane. At these times, 40% or fewer of the volunteers were sufficiently awake to take the test.

up can be recovered as metabolites (inorganic fluoride and conjugated hexafluoroisopropanol).[19,20]

The finding of a more rapid awakening after anesthesia with desflurane confirms the result of two other clinical studies making this comparison[11,12] and is consistent with results from studies in rats.[10] But if the elimination of desflurane only modestly exceeds that of sevoflurane, can this explain the more rapid awakening of volunteers (and patients) given desflurane? More rapid awakening with desflurane does not appear to result from a greater ventilation after anesthesia with desflurane (fig. 2). Nor does it appear to result from a difference in the ratio of MAC_{awake}/MAC because the ratio is 0.33 for both anesthetics.[21,22] The exponential equations resulting from analysis of the data indicate that if awakening from desflurane occurs at 14 min (at an F_A/F_{A0} ratio of 0.17), then awakening from sevoflurane should occur at the same F_A/F_{A0} ratio, with sevoflurane-anesthetized volunteers responding at 20 min; however, they responded at 28 min. That is, the differences in the elimination curves can only explain 43% of the difference in awakening times. An additional fraction of the delay may be explained by the slower tissue elimination that results from the greater brain–blood partition coefficients for sevoflurane, but this would seem an unlikely explanation because the slower elimination of sevoflurane would permit a closer approximation of cerebral and arterial partial pressures.[9]

Theoretically, metabolism of sevoflurane to hexafluoroisopropanol[23] might delay recovery. Hexafluoroisopropanol is a potent anesthetic in rats, with a MAC of 0.00005 atm (*i.e.*, 50 ppm; Z.X. Fang, unpublished data), and has a long terminal half-life.[23] Thus the slower recovery from sevoflurane might, in part, result from the effect of residual sevoflurane combined with the effect of hexafluoroisopropanol. In conflict with this speculation, however, most of this metabolite is conjugated with glucuronide, and we could not detect free hexafluoroisopropanol in the end-tidal gas of volunteers given sevoflurane.

The degradation of sevoflurane to compound A also may contribute to the slower awakening after sevoflurane anesthesia. Compound A appears to bind irreversibly to proteins,[13] and, at high concentrations (350–400 ppm given for 3 h) can produce convulsions and pathologic cerebral changes *after* administration to rats.[24] These thoughts are the basis for our speculation that changes in structure consequent to binding of compound A to cerebral proteins or other tissue constituents might contribute to the slower recovery.

Our finding of a greater incidence of emesis after anesthesia with sevoflurane than with desflurane was unexpected. Similarly, we did not expect to find the suggestion of subjective and interrelated differences in long-term indices of recovery. These differences are not likely due to prolonged anesthesia, which applied equally to desflurane and sevoflurane. Our study did differ from most previous studies that used higher fresh gas flow rates (see Philip *et al.*[3] who used inflow rates of 5 l/min). Such flow rates will produce lower concentrations of compound A than those breathed by the volunteers in our study. Decades ago investigators in this laboratory examined the incidence of vomiting after anesthesia with halothane *versus* isoflurane and found that vomiting was significantly greater after anesthesia with halothane.[25] Although this comparison may be considered flawed because the data were not obtained contemporaneously, they were obtained using compa-

rable experimental conditions, including prolonged anesthesia (6 h with isoflurane and 7.2 h with halothane).[26] Halothane and sevoflurane can be degraded by soda lime to produce unsaturated, toxic compounds,[27,28] whereas isoflurane and desflurane resist such degradation.[29] Perhaps the greater incidence of emesis and the subjective differences in long-term recovery may be a consequence of the binding of compound A to cerebral tissue rather than an effect of sevoflurane *per se*. Confirmation of this speculation requires an *a priori* study rather than the *ad hoc* approach that we used.

We also anticipated that some reductive metabolism of sevoflurane would lead to measurable concentrations of n-pentane, indicating some level of lipid peroxidation. Such a possibility had been suggested by results from *in vitro* studies.[30] Lipid peroxidation might have explained some of the nephrotoxicity and hepatotoxicity seen with compound A.[14,24,31-33] However, we found no production of n-pentane.

We had not anticipated the F_A/F_I and F_A/F_{A0} values obtained with compound A. The F_A/F_I ratio for compound A equaled that expected for a compound having a blood-gas partition coefficient similar to isoflurane,[34] and the ratio was sustained (fig. 5), rather than slowly increasing, as is the case with isoflurane. Although these data are consistent with observations made by other investigators,[35] they are inconsistent with an estimated blood-gas partition coefficient of compound A of approximately 0.3.[13]

Similarly, the F_A/F_{A0} ratio for compound A presented two unexpected findings (fig. 6B). First, the decay was more rapid than would be expected from the duration of exposure to compound A. Second, and more important, the shape of the curve was unexpected, having an initial steep descent and then a prolonged flat portion. That is, the curve did not show the expected exponential (progressively slower) washout of lung, vessel-rich group, and muscle group, as seen for sevoflurane and desflurane (figs. 4 and 6). Instead, we found an initial rapid (1-5 min) elimination (probably from lung) and then a sustained constant low level as from a large reservoir (probably fat). This implies that compound A degrades in or binds to all lean tissues but not fat. This hypothesis is consistent with data we have obtained showing that compound A is degraded by human albumin and hemoglobin.[13]

Administration of 30 mg propofol approximately 10 min before the termination of anesthetic administration may have compromised to some extent our ability to discriminate between the recovery from desflurane *versus* sevoflurane. Similarly, it may have minimized differences in vomiting and the expression of nausea. However, the time to response to command after desflurane and sevoflurane was 14 and 28 min, respectively, after termination of anesthetic administration, and we would argue that by 24-38 min after administration of this small dose of propofol to 82-kg healthy young men, little if any effect of the propofol would remain.

In summary, we find that the inspired concentrations of desflurane and sevoflurane rapidly approach the concentration in end-tidal gas when the end-tidal gas concentration is maintained constant. Consistent with its greater solubility in blood and tissues and with its greater metabolism, the difference between inspired and end-tidal concentrations (as a fraction of the end-tidal concentration) is nearly twice as great for sevoflurane. On the other hand, because of its greater metabolism, elimination of sevoflurane in end-tidal gas is only slightly slower than elimination of desflurane. Despite the smallness of the difference in elimination, short- and long-term awakening is approximately twice as fast with desflurane than with sevoflurane. Slower awakening after anesthesia with sevoflurane may result from slower elimination in end-tidal gas and greater tissue solubility. We speculate that the slower awakening also may result from the effects of degradation products of sevoflurane.

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