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Cerebral Uptake and Elimination of Desflurane, Isoflurane, and Halothane from Rabbit Brain: An In Vivo NMR Study

Stephen H. Lockhart, Ph.D., M.D., Yoram Cohen, Ph.D.,† Nobuhiko Yasuda, M.D.,‡ Beth Freire, B.S.,§ Shahram Taheri, B.S.,§ Lawrence Litt, Ph.D., M.D.,¶ Edmond I. Eger II, M.D.***

The authors used *in vivo* ^{19}F nuclear magnetic resonance spectroscopy to determine rates of cerebral uptake and elimination of desflurane, isoflurane, and halothane in rabbits. After anesthetizing animals by intramuscular and intravenous injection of methohexital and inhalation of 70% nitrous oxide, intravenous and intraarterial catheters were inserted and a tracheostomy and craniotomy performed. Ventilation was controlled to maintain arterial carbon dioxide tension ($P_{a_{CO_2}}$) from between 35 and 45 mmHg. A 2–2.5-cm diameter circle of dura was exposed, over which a 0.9 × 1.0-cm elliptical surface coil was placed. Cerebral anesthetic concentrations (CC) were estimated from spectra acquired on a 4.7-Tesla spectrometer. Alveolar uptake and elimination also were assessed, using inspired (FI) and end-tidal (denoted FA_0 at the end of administration) concentrations measured by gas chromatography. After baseline spectra were obtained, volatile agents were administered for 30 min, followed by a 120-min period of elimination. Our findings demonstrate that cerebral uptake and elimination correlate with solubility: they are most rapid for desflurane, next most rapid for isoflurane, and least rapid for halothane. During administration, cerebral uptake of desflurane ($CC/FI = 0.690 \pm 0.049$ at 9 min) was approximately 1.7 times faster than isoflurane ($CC/FI = 0.691 \pm 0.020$ at 15 min) and 3 times faster than halothane ($CC/FI = 0.662 \pm 0.040$ at 27 min). Similarly, elimination rates for desflurane ($CC/FA_0 = 0.238 \pm 0.015$ at 9 min) were 1.7 times faster than isoflurane ($CC/FA_0 = 0.236 \pm 0.017$ at 15 min) and three times faster than halothane ($CC/FA_0 = 0.212 \pm 0.033$ at 27 min). In the comparison of cerebral and alveolar uptake and elimination, cerebral values parallel alveolar values, with a temporal delay, such that alveolar precedes cerebral. The hysteresis or lag between alveolar and cerebral concentrations is similar for all agents. Our results indicate that anesthetic residence in brain is of shorter duration with desflurane than with isoflurane or halothane, suggesting that recovery from anesthesia should be more rapid. (Key words: Anesthetics, volatile: desflurane; halothane; isoflurane. Measurement techniques, magnetic resonance spectroscopy: ^{19}F. Pharmacokinetics: uptake; elimination.)

* Assistant Professor, Department of Anesthesia; University of California President's Fellow.

† Postdoctoral Fellow, Department of Pharmaceutical Chemistry; Fulbright Scholar.

‡ Fellow, Department of Anesthesia University of California, San Francisco; Assistant Professor, Jikei University, Tokyo, Japan.

§ Research Associate.

¶ Associate Professor of Anesthesiology and Radiology.

** Professor of Anesthesia.

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Address reprint requests to Dr. Lockhart: Department of Anesthesia, Room S-455, Box 0464, University of California, San Francisco, California 94143-0464.

THE LOW SOLUBILITY of desflurane (I-653) in blood[1] (blood–gas partition coefficient of 0.42 in humans) and tissues[2] indicates a rapid elimination and recovery from anesthesia. In fact, desflurane is eliminated from the lungs more rapidly than is isoflurane or halothane,[3,4] suggesting that cerebral elimination should also be more rapid.

Recent studies of the cerebral kinetics of fluorinated anesthetics have applied *in vivo* ^{19}F nuclear magnetic resonance (NMR) spectroscopy and found that this technique provides results for halothane[5] and isoflurane[6] that are consistent with *in vitro* results previously obtained by more invasive methods.[7,8] Despite significant differences in blood solubility between isoflurane and halothane, these NMR data showed little difference in the rates of cerebral elimination. However, these data were not obtained concurrently or under identical conditions. Additionally, the cerebral kinetics of isoflurane and halothane were not directly compared. In this study, we have determined the rate of cerebral uptake and elimination of desflurane and compared these results with those for isoflurane and halothane in rabbits using *in vivo* ^{19}F NMR spectroscopy.

Materials and Methods

With approval from the University of California, San Francisco Committee on Animal Research, we anesthetized six New Zealand White rabbits, weighing 4–5 kg, by intramuscular and intravenous injection of methohexital, inhalation of 70% nitrous oxide, and local infiltration of 1% lidocaine. After insertion of intravenous and intraarterial catheters, a tracheostomy was performed, and ventilation was mechanically controlled to maintain arterial carbon dioxide tension ($P_{a_{CO_2}}$) between 35 and 45 mmHg. A nonrebreathing system was used throughout these studies. Intravascular volume was maintained by infusing lactated Ringer's solution ($4\ ml \cdot kg^{-1} \cdot hr^{-1}$), and paralysis was maintained by infusing pancuronium (2 mg/hr). Blood pressure and heart rate were measured continuously *via* the intraarterial catheter. In each case, we were able to maintain these parameters within 20% of their initial values by administered a bolus of lactated Ringer's (5 ml/kg) at most twice. Rectal temperature was maintained between 37 and 40° C using a servomechanism-controlled water-jacketed cradle. A craniectomy was performed to expose a 2–2.5-cm diameter circle of dura.

After a baseline ^{19}F NMR spectrum was obtained, nitrous oxide administration was discontinued for 10 min.

A square-wave pulse of volatile anesthetic or a combination of anesthetics in oxygen was then administered from premixed tanks for precisely 30 min. Concurrent administration of desflurane, isoflurane, and halothane was not possible because the structure of desflurane (1,2,2,2-tetrafluoroethyl difluoromethyl ether) and isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) differ by only one atom, preventing simultaneous measurement of their cerebral concentrations by *in vivo* NMR spectroscopy. Therefore, volatile agents were administered according to the protocol outlined in table 1. Each of the first three rabbits received a combination of desflurane (4.5%) and halothane (1%) as well as a combination of isoflurane (2%) and halothane (1%), and the order of the two administrations was randomized. During the period of 2 h that separated these anesthetic administrations, anesthesia was maintained with nitrous oxide and methohexital ($3\ mg \cdot kg^{-1} \cdot hr^{-1}$) for the 120 min period of elimination of volatile agent. Cerebral and alveolar rates of elimination for the second administration of halothane were slower than for the first, indicating a residual presence of that agent. Thus, only data from the first administration were included in the analysis.

To improve the signal-to-noise ratio during the latter stages of elimination, we modified the protocol for the three remaining rabbits (table 1). Each agent was given separately in three successive experiments in each rabbit. This allowed the administration of higher concentrations of desflurane (6.7%), isoflurane (4.5%), and halothane (2.5%). Since the comparison of greatest interest was that between desflurane (a new agent) and isoflurane (the most widely used agent), we administered one of these two agents first and halothane second. A period of 2 h separated the administration of desflurane and isoflurane. Half of all animals (three of six) received desflurane before isoflurane, and half received it after.

During administration, NMR spectra were acquired for 6-min epochs with inspired (F_I) and end-tidal (F_A) gas samples obtained at the midpoint of each epoch. One additional F_I and F_A sample were obtained 30 min after the start, immediately before discontinuing administration of the volatile agent(s). During elimination, spectra were collected in 6-min epochs for the first 30 min, in 12-min epochs to 90 min, and in one 30-min epoch to 120 min. F_A samples were obtained at the midpoint of each.

Cerebral concentrations (CC) of desflurane, isoflurane, and halothane were estimated from ^{19}F spectra acquired at 188.2 MHz on a 4.7-Tesla Nalorac® spectrometer. An elliptical (1.0 × 0.9-cm diameter), two-turn radiofrequency surface detection coil with a balanced matched circuit was centered over the exposed dura.[9] A reference bead containing potassium fluoride (KF) in deuterium oxide was placed above the coil and served as both a chemical shift and a numerical integration reference. Magnetic field homogeneity was maximized by adjusting room temperature shimming coils until the water proton line width was less than 35 Hz. A one-pulse sequence with quadrature detection, an acquisition time of 256 ms, and a dwell time of 62.5 μs were used. The spectral width was ±8000 Hz, and 8,000 complex data points were sampled. The pulse width (approximately 40 μs) was chosen to give the maximum signal intensity *in vivo*. Signal intensity was defined as the area of the single peaks for halothane and desflurane or of the trifluoromethyl peak for isoflurane, normalized by the area of the KF reference peak. We have demonstrated previously that variation in estimates of cerebral concentrations using the surface coil methodology described is less than 4% across the range of concentrations studied.[10].

Inspired and alveolar gas samples were taken in 50-ml glass syringes sealed with nylon three-way stopcocks. All gases were analyzed on a Gow Mac® series 580 gas chromatograph with a column composed of 10% SF 96 on Chromasorb W High Performance, 68/80-mesh, 0.32 cm × 6.1 m, maintained at 48° C. A flame ionization detector at 150° C was used. Gas samples from tank standards, previously calibrated using primary standards, were injected into the chromatograph at intervals during each study.

The ratios F_A/F_I and F_A/F_{A_0} defined alveolar uptake and elimination, respectively, where F_{A_0} was the alveolar concentration measured immediately before discontinu-

TABLE 1. Protocol for Administration and Elimination of Volatile Agents

	Time (min)*							
Rabbit	0–30	30–60	60–90	90–120	120–150	150–180	180–210	210–300
1	des 4.5 + hal 1.0	elim (des + hal) ----------→				iso 2.0 + hal 1.0	elim (iso + hal) ----------→	
2	iso 2.0 + hal 1.0	elim (iso + hal) ----------→				des 4.5 + hal 1.0	elim (des + hal) ----------→	
3	des 4.5 + hal 1.0	elim (des + hal) ----------→				iso 2.0 + hal 1.0	elim (iso + hal) ----------→	
4	iso 4.5	elim (iso)	hal 2.5	elim (Hal + Iso)		des 6.7	elim (des + hal)	Elim (Des)
5	des 6.7	elim (des)	hal 2.5	Elim (Hal + Des)		iso 4.5	elim (iso + hal)	Elim (Iso)
6	iso 4.5	elim (iso)	hal 2.5	Elim (Hal + Iso)		des 6.7	elim (des + hal)	Elim (Des)

Concentrations are percent values.
Des = desflurane; iso = isoflurane; hal = halothane; elim = elimination.

* Time represents time from the start of the first administration of volatile agents.

TABLE 2. Cerebral and Alveolar Uptake of Desflurane, Isoflurane, and Halothane

Time (min)	Cerebral (CC/FI)			Alveolar (FA/FI)		
	Desflurane	Isoflurane	Halothane	Desflurane	Isoflurane	Halothane
0–6	0.471 ± 0.031*	0.322 ± 0.011†	0.210 ± 0.009	0.760 ± 0.029‡	0.611 ± 0.039§	0.449 ± 0.049
6–12	0.690 ± 0.049*	0.590 ± 0.029†	0.411 ± 0.029	0.858 ± 0.019‡	0.750 ± 0.029§	0.592 ± 0.049
12–18	0.840 ± 0.021*	0.691 ± 0.020†	0.510 ± 0.037	0.861 ± 0.021‡	0.780 ± 0.030§	0.631 ± 0.047
18–24	0.870 ± 0.028*	0.772 ± 0.008†	0.582 ± 0.030	0.901 ± 0.028‡	0.810 ± 0.019§	0.660 ± 0.039
24–30	0.902 ± 0.010*	0.822 ± 0.020†	0.662 ± 0.040	0.903 ± 0.010‡	0.821 ± 0.020§	0.681 ± 0.050

All values are mean ± SE, n = 6.

* Differs significantly from cerebral values for isoflurane and halothane during the same time interval.

† Differs significantly from cerebral values for halothane during the same time interval.

‡ Differs significantly from alveolar values for isoflurane and halothane during the same time interval.

§ Differs significantly from alveolar values for halothane during the same time interval.

ing administration of the agent. For the purposes of this experiment, we assumed that the cerebral concentration of anesthetic (measured by NMR) was proportional to the cerebral partial pressure (*i.e.*, that Henry's Law was obeyed).[11] We also assumed that end-tidal, arterial, and cerebral partial pressures were equal after 30 min of equilibration; *i.e.*, CC (at 30 min) = FA_0. Cerebral uptake and elimination were then defined by the ratios CC/FI and CC/FA_0, respectively.

Pharmacodynamic models of hysteresis describe the relationship between the concentration of a drug (in the compartment from which samples are obtained) and its effect. Even if the action of a drug at its effect site is instantaneous, delays can occur between the time at which a given concentration is reached in the sampling compartment and the time at which it is reached at the effect site. This time lag is referred to as distributional hysteresis. In our study, hysteresis is defined as the lag between the attainment of a given alveolar (sampling compartment) and cerebral (effect site) anesthetic partial pressure. For each agent we have assumed that the maximum cerebral concentration and the maximum alveolar concentration (both achieved after 30 min of administration) were equal. A plot of the alveolar concentration (as a proportion of its maximum value) *versus* the cerebral concentration (as a proportion of its maximum value) obtained during each sampling interval provides a graphic representation of hysteresis. In the absence of hysteresis, alveolar and cerebral concentrations should be equal at all times during anesthetic administration and elimination, resulting in a linear relationship. In contrast, hysteresis results in a curvilinear relationship in which values are equal only at the end of anesthetic administration.

Results

Cerebral and alveolar uptake and elimination were most rapid with desflurane, next most rapid with isoflurane, and least rapid with halothane (tables 2 and 3). The

TABLE 3. Cerebral and Alveolar Elimination of Desflurane, Isoflurane, and Halothane

Time (min)	Cerebral (CC/FA_0)			Alveolar (FA/FA_0)		
	Desflurane	Isoflurane	Halothane	Desflurane	Isoflurane	Halothane
0–6	0.517 ± 0.028*	0.686 ± 0.035	0.729 ± 0.045	0.175 ± 0.020‡	0.242 ± 0.021	0.282 ± 0.019
6–12	0.238 ± 0.015*	0.337 ± 0.019	0.403 ± 0.035	0.071 ± 0.030‡	0.102 ± 0.010	0.140 ± 0.010
12–18	0.158 ± 0.020*	0.236 ± 0.017	0.302 ± 0.031	0.050 ± 0.010§	0.072 ± 0.010	0.099 ± 0.009
18–24	0.114 ± 0.009*	0.180 ± 0.017	0.248 ± 0.024	0.041 ± 0.010§	0.056 ± 0.009	0.080 ± 0.008
24–30	0.077 ± 0.016*	0.136 ± 0.013	0.212 ± 0.033	0.034 ± 0.010§	0.047 ± 0.009	0.067 ± 0.008
30–42	0.063 ± 0.011	0.101 ± 0.006	0.162 ± 0.022	0.026 ± 0.007§	0.039 ± 0.006	0.055 ± 0.009
42–54	0.049 ± 0.005	0.098 ± 0.012	0.154 ± 0.006	0.019 ± 0.003§	0.030 ± 0.004	0.045 ± 0.009
54–66	0.030†	0.088 ± 0.010	0.127 ± 0.006	0.017 ± 0.003§	0.024 ± 0.001	0.039 ± 0.001
66–78		0.077 ± 0.013	0.084 ± 0.006	0.014 ± 0.001	0.019 ± 0.001	0.035 ± 0.006
78–90		0.059 ± 0.007	0.072 ± 0.003	0.013 ± 0.001	0.017 ± 0.001	0.032 ± 0.005
90–120		0.048 ± 0.005	0.074 ± 0.004	0.009 ± 0.001	0.017 ± 0.001	0.027 ± 0.001

All values are mean ± SE. For all determinations for which standard errors are reported, n = 6.

* Differs significantly compared with cerebral values for isoflurane and halothane during the same time interval.

† Values obtained in only one animal. Hence standard error not reported.

‡ Differs significantly compared with alveolar values for isoflurane and halothane during the same time interval.

§ Differs significantly compared with alveolar values for halothane during the same time interval.

cerebral elimination curves (CC/FA_0) (fig. 1) resembled alveolar elimination curves (FA/FA_0) (fig. 2) but with a temporal delay, alveolar elimination always preceding cerebral. The hysteresis (fig. 3) did not differ quantitatively among the three agents.

Our *in vivo* ^{19}F NMR spectra for halothane and isoflurane were consistent with those previously described.[5,6] Halothane produced a single peak with a chemical shift of ≈45 parts per million (ppm) downfield from KF; isoflurane produced two peaks with chemical shifts of ≈41 ppm (trifluromethyl nuclei) and ≈35 ppm (difluroethyl nuclei) downfield from KF. Our results indicate that *in vivo*, desflurane produces a single peak at ≈37.5 ppm downfield from KF. Figure 4 provides representative spectra for the three agents at the end of anesthetic administration and during the first 18 min of elimination.

Discussion

As predicted from their blood solubilities, alveolar uptake and elimination were most rapid with desflurane, next most rapid with isoflurane, and least rapid with halothane. Our findings are consistent with those from comparative studies of alveolar kinetics of these agents in swine and humans.[12,13] Also as predicted, rates for cerebral uptake and elimination resembled alveolar rates. The increase in anesthetic partial pressure during administration and the decrease during elimination were more rapid for alveolar than for cerebral partial pressures. The hysteresis, or the lag between the attainment of a specified anesthetic partial pressure in arterial blood and its attainment in the brain, was similar for all three agents. Our *in vivo* ^{19}F NMR spectroscopy measurements are consistent with a more rapid recovery from anesthesia with desflurane than with isoflurane or halothane, and a more rapid recovery from anesthesia with isoflurane than with halothane. This ranking has been documented in rats.[14]

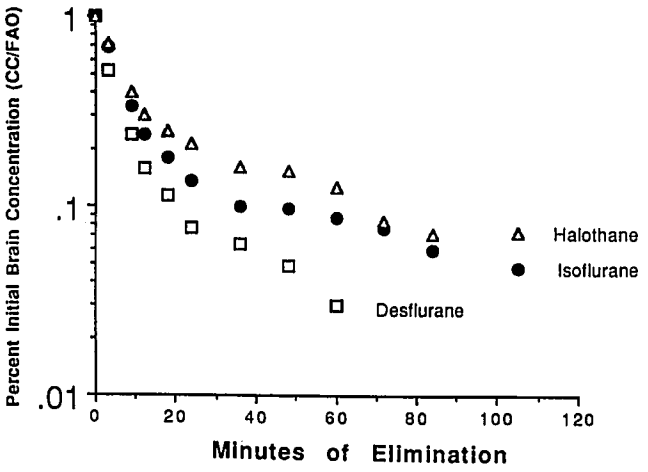

FIG. 1. Cerebral elimination (CC/FA_0) for desflurane is more rapid than isoflurane, which in turn is more rapid than halothane (mean of six determinations).

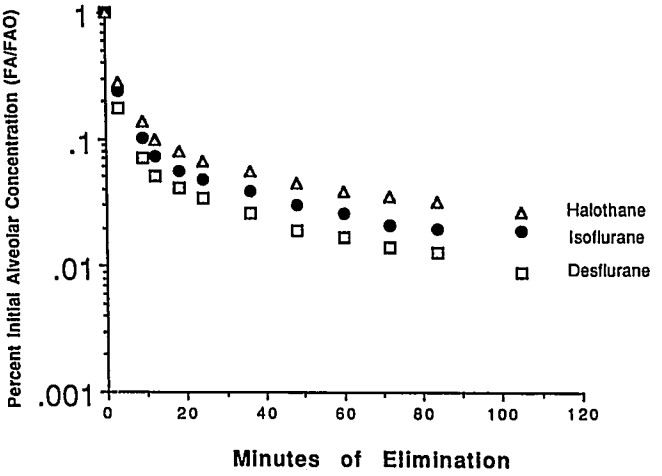

FIG. 2. Alveolar elimination (FA/FA_0) for desflurane is more rapid than isoflurane, which in turn is more rapid than halothane (mean of six determinations).

In order to define cerebral uptake (CC/F_I) and elimination (CC/FA_0) in a manner comparable to alveolar uptake (FA/F_I) and elimination (FA/FA_0), we assumed that cerebral and alveolar concentrations were equal after 30 min of administration of the volatile agents. However, with more soluble agents (isoflurane and halothane), FA increases at a greater rate during the final minutes of anesthetic administration than with less soluble agents

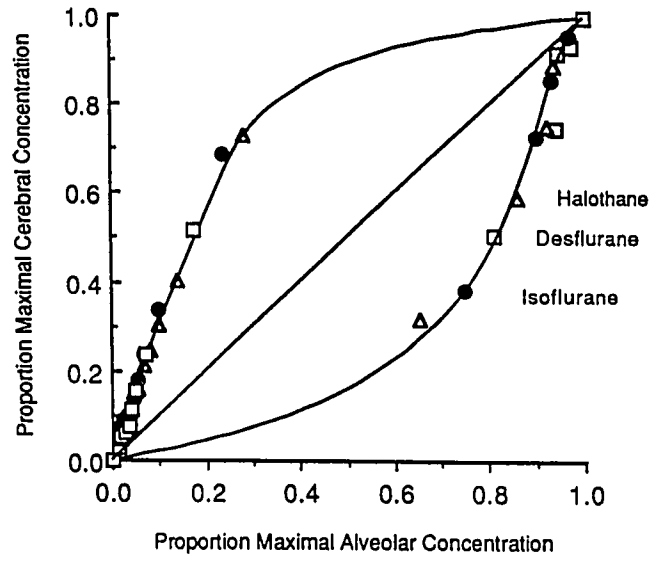

FIG. 3. The increase in anesthetic partial pressure during administration and its decrease during elimination were more rapid for alveolar than for cerebral partial pressures. The hysteresis described was similar for all three agents. The linear relationship that would be observed in the absence of hysteresis is represented by the line connecting the points (0,0) and (1,1).

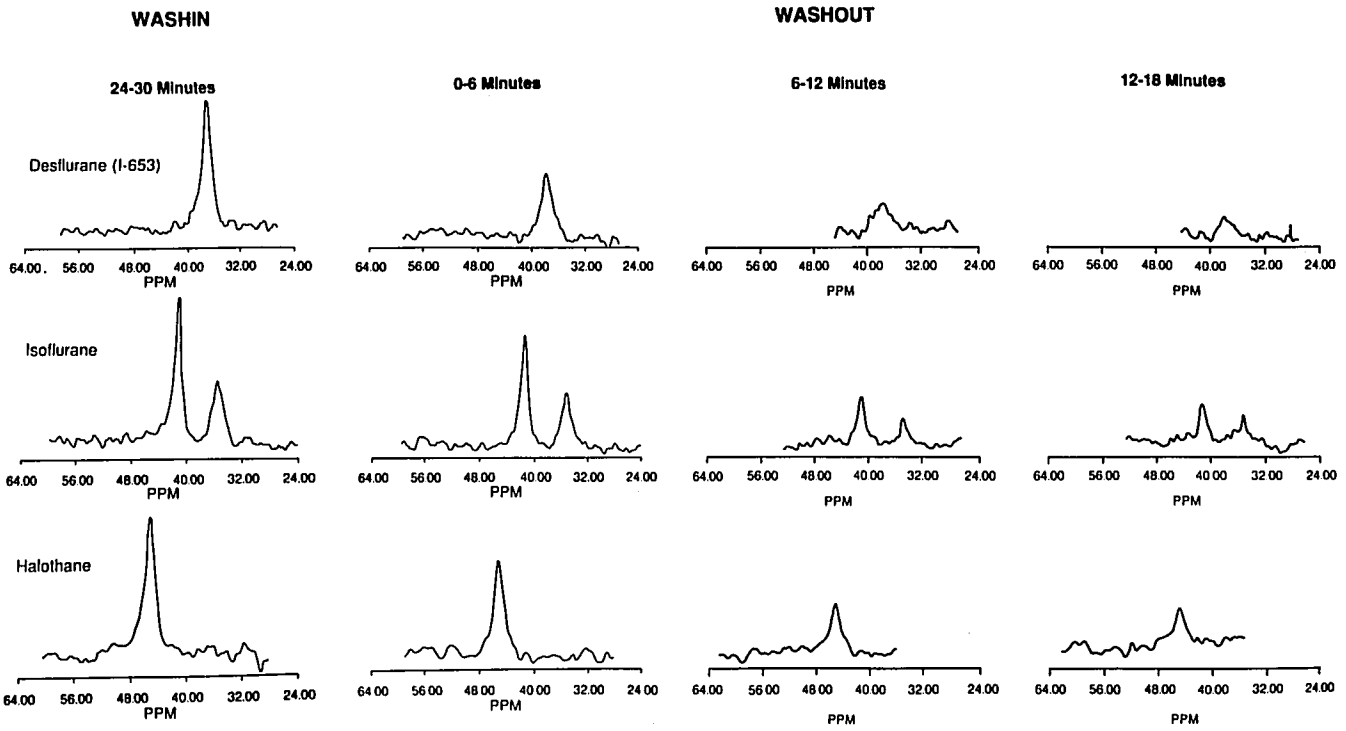

FIG. 4. Representative spectra for desflurane, isoflurane, and halothane at the end of administration and during the first 18 min of elimination. The x-axis denotes chemical shift in parts per million (ppm) downfield from potassium fluoride, which served both as a chemical shift and numerical integration reference.

(desflurane). As a result, the partial pressure of anesthetic in arterial blood perfusing the brain increases for halothane (and to a lesser extent for isoflurane) but is relatively stable for desflurane. Cerebral and alveolar concentrations should be nearly identical for all agents, but we would expect values for desflurane to be closest. The assumption that CC = F_{A_0} at 30 min for all agents may provide artificially increased elimination rates for halothane and isoflurane when compared with desflurane. Thus, the actual difference in elimination rates may be slightly greater than reported.

It was necessary to use epochs at least 6 min to acquire NMR data sufficient to compute cerebral anesthetic concentrations during administration and elimination. From these data, we determined cerebral concentrations and assumed that these concentrations represented the actual concentrations at the midpoint of each epoch. However, this method may slightly underestimate the true cerebral concentration during uptake and overestimate it during elimination. Deviations would be greatest for desflurane, the agent whose concentration increases most rapidly during administration and decreases most rapidly during elimination. As a result, the magnitude of differences between the rates of uptake and elimination of desflurane compared with isoflurane and halothane may be further underestimated.

To avoid problems with spatial localization experienced with larger coils,[5,6,15] we used a 1 × 0.9-cm elliptical surface coil centered over exposed dura to estimate elimination rates more accurately. The cerebral elimination rates we observed for isoflurane (half life [$t_{1/2}$] = 8 min) were two to four times faster than those reported by Strum *et al.* ($t_{1/2}$ = 18 min)[7] and by Mills *et al.* ($t_{1/2}$ = 36 min),[6] probably because these investigators administered anesthesia for 90 min, compared to 30 min in our study. The greater duration allows for greater uptake by compartments with longer rate constants. In the absence of a definition of the entire elimination curve, more weight may be applied to what appears to be the terminal portion of the curve, resulting in a longer alveolar and, therefore, cerebral elimination half life.

In summary, our results indicate that uptake by and elimination from cerebral tissues are more rapid with desflurane than with isoflurane or halothane. Accordingly, recovery from anesthesia with this new agent is expected to be more rapid.

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