Anesthesiology
54:3–8, 1981

Relationship of Concentrations of Halothane and Enflurane to Their Metabolism and Elimination in Man

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In order to assess the impact of anesthetic metabolism on elimination of halothane and enflurane, three groups of healthy, lean young men were given enflurane and halothane concomitantly for two hours. Six awake volunteers (Group I) breathed 0.21 per cent enflurane and 0.11 per cent halothane in air. Four surgical patients (Group II) breathed the same anesthetic concentrations with 70 per cent N_2O. Five more surgical patients (Group III) breathed these volatile agents in concentrations that were four times greater, also in 70 per cent N_2O. All surgical patients received anesthetic adjuvant drugs (morphine, diazepam, thiopental, and pancuronium) as clinically indicated. End-tidal and inspired anesthetic concentrations were measured during anesthetic administration and for three to five days thereafter. Anesthetic uptake, elimination, and metabolism were calculated.

Data from Groups I and II were comparable. Forty-five per cent of the halothane and 90 per cent of the enflurane taken up were recovered. The smaller recovery of halothane was associated with a more rapid reduction in the end-tidal concentration of halothane than enflurane at the end of anesthesia. Group III differed from Groups I and II in that significantly more halothane (59 per cent) was recovered, while 90 per cent of enflurane was again recovered. In addition, for the first 30 to 205 min of elimination, the halothane end-tidal concentration decreased more slowly than did the enflurane end-tidal concentration.

We conclude that a greater fraction of the halothane taken up at subanesthetizing, as opposed to anesthetizing, concentrations is metabolized. This difference explains why elimination of halothane at subanesthetizing concentrations is more rapid than is elimination of enflurane, a less soluble but also less easily metabolized agent. Indeed, the absolute or total amount of drug metabolized was greater in the higher-concentration study (Group III), only the relative percentage of drug taken up that was not recovered (a measure of the percentage metabolized) was smaller. Furthermore, in this study, nitrous oxide and the anesthetic adjuvants morphine, diazepam, thiopental, and pancuronium had no significant effect on the extent of halothane or enflurane metabolism. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: halothane; enflurane. Biotransformation (drug). Pharmacokinetics. Recovery.)

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Received from the Department of Anesthesia, University of California, San Francisco, California 94143. Accepted for publication June 30, 1980. Supported in part by USPHS Grant GM15571 and the Anesthesia Research Foundation.

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THE RATE at which the fractional alveolar concentration (F_A) of an anesthetic approaches its inspired concentration (F_I) varies inversely with its solubility in blood. Similarly, the rate of elimination [F_A divided by the end-tidal concentration (F_{AO}) at the moment at which anesthetic administration is discontinued] also varies inversely with solubility.[1] Thus, the F_A/F_{AO} curve should decay more rapidly for enflurane (blood-gas partition coefficient 1.8) than for halothane (blood-gas partition coefficient 2.3).

These predictions were supported by the results of Torri *et al.*[2] Munson *et al.*[3] found similar results during the uptake period at trace doses of enflurane and halothane. However, Munson *et al.*[3] and Klan *et al.*[4] found that halothane was eliminated more rapidly than enflurane. Both Munson and Klan suggested that the more rapid elimination of halothane resulted from a greater metabolism of halothane.

The apparent discrepancy between these results might be explained by the effects of the experimental circumstances on the metabolism of halothane. Both Torri and Munson studied elimination after simultaneous administration of enflurane and halothane. However, Torri used concentrations that were anesthetizing, while Munson administered trace levels. In addition, Torri studied elimination while anesthesia was continued with nitrous oxide; Munson and Klan studied elimination in the absence of significant concentrations of nitrous oxide. Thus, these studies are distinguished by the concentrations of enflurane and halothane that were administered, and by the presence or absence of nitrous oxide. The significance of such factors is suggested by the results of previous reports. Sawyer *et al.*[5] found that anesthetic metabolism becomes independent of the concentration when those concentrations exceed 2–10 per cent of MAC. At anesthetizing doses, hepatic enzyme systems presumably are saturated, and anesthetic metabolism becomes an insignificant component of uptake or elimination. Thus, the differences in the levels of halothane and enflurane might explain the apparent discrepancy between Torri's results and those of Munson and Klan.

The presence or absence of nitrous oxide also might explain the discrepancy. Umeda and Inaba[6] found that ether inhibits the metabolism of phenytoin. Amess *et al.*[7] demonstrated in man that nitrous oxide can inhibit enzyme systems dependent on vitamin B_{12}. Perhaps in Torri's study the nitrous oxide inhibited anesthetic metabolism and thus allowed the elimination of the agents to proceed as dictated solely by their solubilities.

The following study tests these speculations, particularly the effects of anesthetic concentration and the presence of nitrous oxide on anesthetic metabolism and elimination.

Methods

This study was approved by the Committee on Human Research at the University of California, San Francisco; informed consent was obtained from each subject. We studied three groups of healthy, lean young men. Group I consisted of six volunteer subjects, awake and in the sitting position, who breathed simultaneously 0.21 per cent enflurane and 0.11 per cent halothane in 30 per cent O_2. Group II consisted of four supine patients who breathed the same concentrations of enflurane and halothane in a 30 per cent O_2 and 70 per cent N_2O mixture as part of their surgical anesthesia. Group III consisted of five more patients who breathed, as part of their surgical anesthesia, concentrations of the volatile agents that were four times larger: 0.87 per cent enflurane and 0.43 per cent halothane, also in a 30 per cent O_2 and 70 per cent N_2O atmosphere. The patients were premedicated orally with diazepam (5–10 mg) and intramuscularly with morphine (0–10 mg). Anesthesia was induced with thiopental (200–800 mg), and 70 per cent nitrous oxide was added to provide a basal, background level of anesthesia. Pancuronium (6–10 mg) facilitated endotracheal intubation. Nitrous oxide administration was begun approximately 20–30 min before halothane and enflurane administration commenced. Additional morphine (9–35 mg), thiopental (50–150 mg), and pancuronium (0–6 mg) were given as necessary. Surgery consisted of uncomplicated procedures entailing little or no blood loss.

All groups received these approximately equipotent doses of anesthetics simultaneously for two hours from premixed gas in calibrated cylinders. Subjects in the awake group (I) breathed the gases from a reservoir via a low-resistance nonrebreathing valve and an airtight mouthpiece used in conjunction with a nose clip. Expired gases were delivered through a mixing chamber to a Collins spirometer. A similar system was used for the Group II and Group III patients, except that the nonrebreathing valve was connected to the endotracheal tube, and expired ventilation was measured with a Wright's respirometer. Ventilation was supported with an Airshield volume ventilator (mean $Pa_{CO_2} \pm$ SD, 40.6 ± 4.3 torr). Esophageal or nasopharyngeal temperatures were monitored intraoperatively and showed a prompt and nonprogressive decrease to a mean of 35.3 C (SD, ±0.5 C).

In all subjects, after 1, 2.5, 5, 10, 15, 30, 45, 60, 75, 90, 105, and 120 min of uptake (and at the same time periods plus 150, 180, 240, 360, 1400, 2500, 4000 min and, in some cases, longer during elimination), four variables were meaured: end-tidal, mixed expired, and inspired gas concentrations, and minute ventilation. Although halothane and enflurane were discontinued at the end of two hours, nitrous oxide was administered for longer periods, (75 to 240 min longer, as necessitated by the length of the surgical procedure). In Groups II and III, the use of positive-pressure ventilation necessitated the empirical, separately determined correction of the measured ventilation to account for a compression volume.

A Tracor Model 550 gas chromatograph was used for separation and detection of halothane and enflurane. A 10 per cent S.F. 96 on Chromosorb® WHP, 68/80-mesh, ⅛ inch-by-120-cm column was maintained at 58 C. A nitrogen carrier flow rate of 80 ml/min delivered the sample through the column to a flame ionization detector at 192 C, supplied by 40 ml/min hydrogen and 283 ml/min air. Column retention times were 60 sec for enflurane and 85 sec for halothane.

Calibration of the chromatograph was done with standards at each order of concentration magnitude unless any alinearity was found, whereupon additional standards were prepared. Each calibration point was determined by the arithmetic mean of the peak heights of at least two to four calibration peaks. The standards were prepared in E cylinders, and thus their concentrations remained constant throughout the study. We found remarkable reproducibility of each standard peak throughout any single study day. For example, during a typical (Group II, Patient 3) two-hour period of administration of volatile agents, 12 calibration peaks were run with variances (standard deviation/mean peak height × 100) of 0.38 per cent (enflurane) and 0.3 per cent (halothane). The accuracy of our analysis is demonstrated by the consistency with which the very lowest end-tidal concentrations of enflurane (1.69×10^{-5} per cent) and halothane (1.11×10^{-6} per cent) were measured. Four end-tidal concentrations

were collected (Group I, Volunteer 6, 4180 min) with variances of 4.37 per cent (enflurane) and 7.42 per cent (halothane).

To ensure that we were not measuring contaminants in the collection apparatus, all tubing and glassware were purged with fresh gas (air or oxygen), and controls were tested to demonstrate negligible levels of such contaminants prior to the collection of low-concentration samples. Each subject had control end-tidal samples collected prior to breathing any anesthetic. These control samples were analyzed at the lowest attenuations possible and provided chromatographic traces that were used to determine signal-to-noise ratios at the lowest-concentration samples. In the above example, the signal-to-noise ratios were 5:1 (enflurane) and 6:1 (halothane), and were the smallest accepted in this study.

Anesthetic uptake or elimination in ml/min at a particular sample time was computed by multiplying minute ventilation times the difference between inspired and mixed expired concentrations. The uptake and elimination data were plotted against time, and the resulting points were "fit" by computer to a "best curve" of multiexponential decay (fig. 1). Integrating the multiexponential equation for uptake from zero to 120 min yielded total anesthetic uptake in milliliters. Integrating the elimination equation from zero to infinity yielded the total anesthetic recovered in milliliters. The difference between total uptake (U_T) and total recovery (R_T) was assumed to be due to anesthetic metabolism.

Very small but measurable concentrations of the volatile agents were found during the initial period of elimination in the inspired gas of the nonrebreathing circuit used with Groups II and III. This contamination probably represented anesthetic washout from the inspiratory tubing. The concentration of the contaminants was subtracted from the temporally corresponding end-tidal or mixed expired concentrations. The correction resulted in less than a tenth of a per cent decrease in total anesthetic recovered.

Calibration of the Wright's respirometer against the volume spirometer showed consistent and accurate performance of the respirometer in the presence or absence of 70 per cent N_2O. However, malfunctioning of the respirometer necessitated transport of the final subject (Group III) to the laboratory for measurement of his resting minute ventilation with the Collins spirometer.

As may be apparent, this study was in fact two studies: one in which we asked whether a background of nitrous oxide affected the relative pharmacokinetics

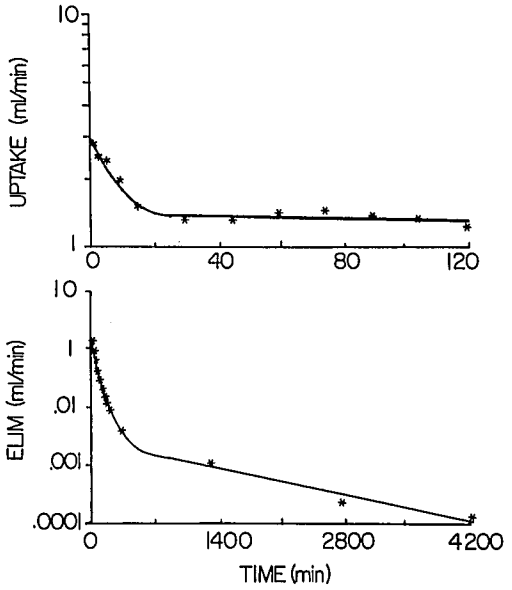

FIG. 1. Representative multiexponential "best-fit" curves of actual data (Patient 4, Group II) for halothane uptake (*upper curve*) and elimination (*lower curve*). Computer-assisted fitting by a nonlinear least-squares analysis was used.

of enflurane and halothane; and a second, in which we asked whether increases in the concentrations of enflurane and halothane (in the presence of a constant anesthetic background) affected their relative pharmacokinetics. We compared Groups I and II to answer the first question, and Groups II and III to answer the second. A t test for unpaired data was used in both cases, and $P < 0.05$ was accepted as significant.

Results

During the two hours of uptake, comparable curves of F_A/F_I plotted against time were obtained for all three groups for both enflurane and halothane (fig. 2). In contrast, curves representing elimination showed two distinctly different patterns. In Groups I and II, the F_A/F_{A0} ratios for halothane decreased consistently more rapidly than did the ratios for enflurane (*upper half*, fig. 3). For all members of Group III, enflurane's F_A/F_{A0} ratio fell more rapidly until 30 to 205 min, after which time the halothane F_A/F_{A0} ratio became equal to then consistently less than, the enflurane ratio (*lower half*, fig. 3). This crossover point occurred at subanesthetic concentrations of halothane (0.0075 to 0.033 per cent) and enflurane (0.082 to 0.079 per cent), concentrations comparable to those found in the initial portions of the elimination curves for Groups I and II.

Virtually identical fractions of the enflurane taken up appeared to be metabolized in all three groups; that

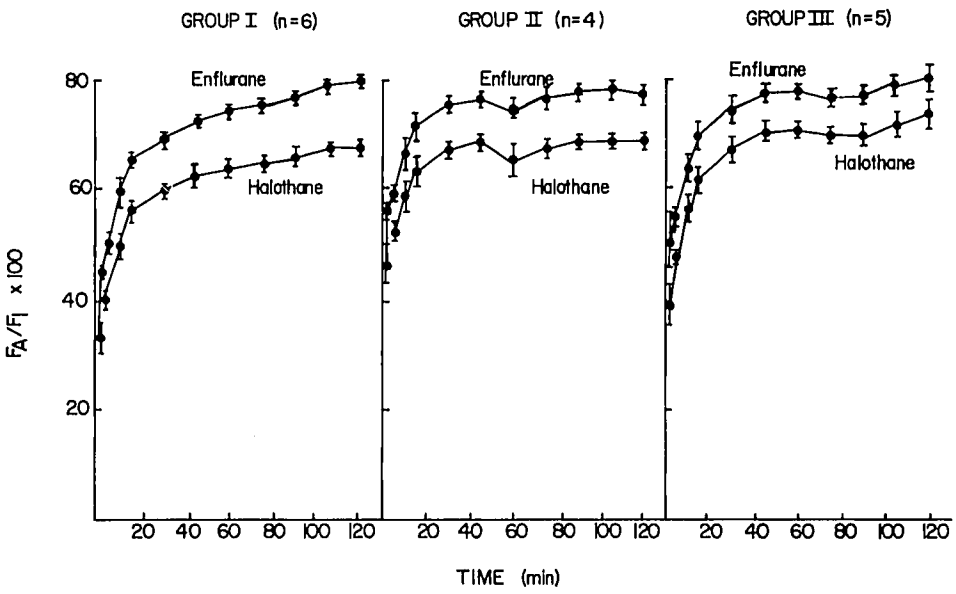

FIG. 2. The alveolar-to-inspired ratio (F_A/F_I) curves for halothane and enflurane illustrate comparable data (mean ± SEM) for all three groups during the uptake period.

is, values of $(U_T - R_T/U_T)$ were the same. In contrast, with halothane this fraction decreased as the inspired halothane concentration was changed from 0.1 per cent (Group II) to 0.4 per cent (Group III) (table 1).

Discussion

Our results at least qualitatively explain the apparent discrepancy between the results of Torri *et al.*[2] on the one hand and those of Munson *et al.*[3] and Klan *et al.*[4] on the other. We found that at the higher anesthetic concentrations used in clinical practice, metabolism plays a smaller role in the rate at which elimination occurs, thereby permitting solubility to play a more important role. The metabolic effect applies differentially to halothane and enflurane, since metabolism of halothane is inherently greater at any given MAC. Therefore, Torri's use of anesthetizing concen-

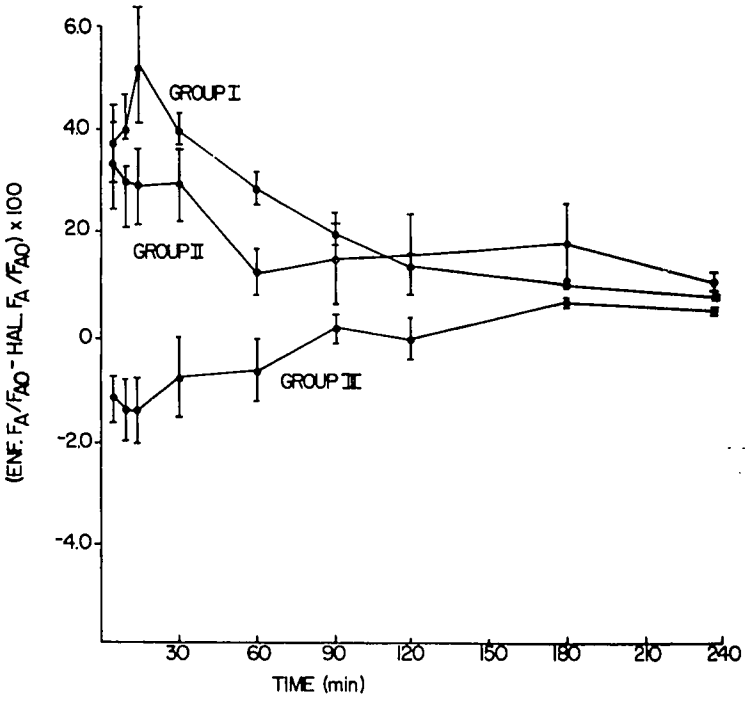

FIG. 3. The differences (mean ± SEM) among the F_A/F_{AO} values for enflurane and for halothane, plotted for the three groups. Groups I and II were comparable and had more rapid elimination of halothane than did Group III, which initially had more rapid elimination of enflurane. F_A/F_{AO} is the ratio, during elimination, of the alveolar concentration at a subsequent time to the alveolar concentration at the moment the anesthetic administration was discontinued.

trations of halothane should have retarded the elimination of halothane more than was the case in the Munson and Klan studies.

The presence of nitrous oxide and other drugs in Group II did not appear to affect the metabolism of either enflurane or halothane. Thus, our results do not support the thesis that nitrous oxide and other drugs commonly used in anesthesia may influence the rate of recovery from halothane or enflurane through an influence on their metabolism.

The implication of these data may explain more than an apparent discrepancy in the literature. Our results suggest that the elimination of halothane is significantly influenced by metabolism, and that this influence increases as lower anesthetic partial pressures are reached. However, we made no measure of a more rapid clinical recovery that may have resulted from this metabolism-enhanced halothane elimination. Since this effect on halothane elimination was not pronounced until trace levels of the anesthetics were reached, certainly no obvious differences in recovery are expected. Our results also suggest that the simultaneous use of nitrous oxide, narcotics, barbiturates, pancuronium, and diazepam does not significantly alter the impact of anesthetic metabolism on the elimination of halothane or enflurane.

In agreement with other work, we have shown that metabolism of halothane accounts for a far greater fraction of halothane uptake than is the case with enflurane.[8,9] The accuracy of our method of measurement of uptake and elimination is suggested by the smallness of the standard errors we obtained (table 1). However, we may have overestimated anesthetic metabolism, since our method is an indirect one dependent on the accurate measurement of uptake and elimination. For example, we did not account for losses of either agent via skin, urine, or feces. Percutaneous loss of halothane has been measured in other studies,[10] suggesting only a small fraction of 1 per cent of the halothane taken up could be accounted for by this mechanism. Similarly, loss through urine (and feces) can be discounted because the solubilities of both halothane and enflurane in aqueous solutions are low,[1] and because such a loss would occur in these studies when the anesthetic partial pressure was very low (hours after anesthetic administration was discontinued). Finally, perhaps recovery was not measured for a sufficiently long period, and thereby tissues that have long time constants were not included. However, the only tissue that this argument might apply to is fat. The time constants for fat may be estimated as two days for halothane and a slightly shorter period for enflurane.[1] Thus, monitoring recovery for four days should produce a reasonably accurate estimate. We therefore conclude that the amount of anesthetic not recovered is a measure of the amount metabolized.

TABLE 1. Percentages of Enflurane and Halothane Metabolized (Mean ± SE)

	n	Per Cent Metabolized*	
		Enflurane	Halothane
Group I	6	10.3 ± 0.9	54.8 ± 1.0
Group II	4	9.3 ± 4.7	55.2 ± 5.9
Group III	5	9.5 ± 3.0	41.3 ± 3.9†

* 100 $(U_T - R_T)/U_T$, where U_T = total uptake; R_T = total recovery.
† A significantly smaller fraction of the halothane administered was metabolized in Group III ($P < 0.05$).

Enflurane is less soluble and less extensively metabolized than is halothane, and thus at clinically used concentrations, enflurane is taken up and eliminated more rapidly than is halothane. Even with the low clinical doses inspired in this study, we were unable to document a significant impact of anesthetic metabolism on the maintenance of the alveolar concentrations. However, at subanesthetic, equipotent concentrations, there occurs a point at which halothane's metabolism becomes the predominant factor in determining the relative rates of halothane and enflurane elimination. The crossover point of the elimination curves occurs at a level of halothane concentration (0.0075 to 0.033 per cent of 1 atmosphere) at which previous animal studies document the onset of dose-dependent hepatic metabolism.[5]

Finally, our estimate of halothane metabolism as a percentage of dose administered is higher than previously published figures.[9] This might be expected since our inspired concentrations, even in Group III, were considerably below concentrations clinically used. In order to administer the agents simultaneously, we could not safely use a full clinical concentration of each. Our 9 to 10 per cent estimate of enflurane metabolism agrees with the 12.5 per cent figure obtained by Chase *et al.*,[11] who used a similar technique.

Enflurane (Ethrane) for these studies was donated by Ohio Medical Products. Halothane (Fluothane) was given by Ayerst Laboratories.

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