The Extent of Metabolism of Inhaled Anesthetics in Humans

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To determine the percentage of anesthetic metabolized and to assess the role of metabolism in the total elimination of inhaled anesthetics, the authors administered isoflurane, enflurane, halothane, and methoxyflurane simultaneously, for 2 h, to nine healthy patients. Total anesthetic uptake during the 2 h of washin and total recovery of unchanged anesthetic in exhaled gases during 5 to 9 days of washout were measured, and from these the per cent of anesthetic uptake that was recovered was calculated. Of the isoflurane taken up, 93 ± 4% (mean ± SE) was recovered. To compensate for factors other than metabolism that limit complete recovery of unchanged anesthetic, the percentage recovery of each anesthetic was normalized to the percentage recovery of isoflurane (which it was assumed undergoes no metabolism). Deficits in normalized recovery were assumed to be due to metabolism of the anesthetics. The resulting estimates of metabolism of anesthetic taken up were: enflurane 8.5 ± 1.0%, halothane 46.1 ± 0.9%, and methoxyflurane 75.3 ± 1.6%. These results indicate that elimination is primarily via the lungs for isoflurane and enflurane, equally via the lungs and via metabolism for halothane, and primarily via metabolism for methoxyflurane. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane; methoxyflurane. Metabolism, drug. Pharmacokinetics. Recovery, drug.)

METABOLISM OF INHALED anesthetics is of interest for at least two reasons. First, metabolism may produce toxic metabolites. Second, metabolism may be an important route of anesthetic elimination. Most studies of anesthetic metabolism have focused on the pathways of metabolism or on the production of metabolites, particularly the production of potentially toxic metabolites.[1–4] Studies of metabolite production, however, may not accurately define the effect of metabolism on total anesthetic elimination. Because recovery of metabolites is incomplete, such studies likely underestimate the total amount metabolized, and thus underestimate the amount eliminated by me-

tabolism. For example, in rats and mice only 50% of the free fluoride produced by metabolism of enflurane or methoxyflurane can be recovered in urine; the rest disappears into bone.[5] Estimates of metabolism based on inorganic fluoride excretion in urine must compensate for the loss to bone by multiplying urinary excretion by a correction factor (usually 2). This correction factor produces, at best, a rough correction. Likewise, only 58–74% of the radioactive label could be recovered in exhaled gases, urine, sweat, and feces in nine humans after the injection of radioactive-labeled halothane.[6] Furthermore, most studies measure the production of only one metabolite.[3,4,7] However, metabolism of anesthetics may produce numerous metabolites by several pathways, with an unknown stoichiometry for the metabolites.

Measurement of mass balance may assess total metabolism of anesthetics more accurately than measurement of metabolites. For an assessment of metabolism by mass balance, the total anesthetic recovered in exhaled gases after anesthetic administration is compared with the total taken up during administration. The difference is assumed to be due to metabolism of the anesthetic. Advantages of mass balance studies are that knowledge of metabolite pharmacokinetics and identification and collection of metabolites are not necessary. A disadvantage is that loss of anesthetic through the wound, across the skin, in urine, and in feces may prevent complete recovery, and these losses would be construed as due to metabolism. Loss of anesthetic across the skin, in urine, in feces, and in sweat has been found to be slight.[6,8] However, loss through the wound may be appreciable, especially if the wound surface is large and highly perfused (e.g., surgery in which the bowel is exposed).

In both mass balance and metabolite recovery studies, differences among patients (e.g., differences in wound size, blood loss, circulation, or respiration) increase the variability of the estimate of metabolism. These differences contribute variability (i.e., they add "noise") to a comparison of results for different anesthetics when such results are obtained in different patients.

In this study, we administered isoflurane, enflurane, halothane, and methoxyflurane simultaneously. We measured the mass balance of each inhaled anesthetic to determine the percentage of anesthetic that is metabolized and assess the role of metabolism in their total elimination. The percentages of the four anesthetics metabolized were compared with each other in each patient. This method increases the power and accuracy of our interanesthetic

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comparisons by eliminating variations in circulation and ventilation as factors that can differentially affect anesthetic uptake, distribution, and elimination. That is, any change in ventilation, cardiac output, or the distribution of blood flow applied equally to all anesthetics.

Materials and Methods

We studied nine young (39 ± 12 yr-old, mean ± SD), healthy patients of average height (170 ± 6 cm) and weight (73 ± 11.1 kg). Four were men and five were women, each undergoing uneventful donor nephrectomies. Our investigation was approved by the Committee on Human Research at the University of California, San Francisco. Informed consent was obtained from each subject.

All patients received morphine and diazepam as premedication. Anesthesia was induced with thiopental and fentanyl. Pancuronium or vecuronium was given to facilitate endotracheal intubation and maintain relaxation. Patients were ventilated *via* a nonrebreathing circuit to produce a normal end-tidal partial pressure of carbon dioxide as determined by mass spectrometry. The inspired gas was then changed from 100% O_2 to 65-70% N_2O, balance O_2. Inspired and end-tidal N_2O concentrations were measured by mass spectrometry. The end-tidal partial pressure of N_2O was 98% of the inspired concentration after 30 min of equilibration.

After 30 min of equilibration with N_2O, a mixture of potent inhaled anesthetics (isoflurane, 0.348 ± 0.021%; enflurane, 0.518 ± 0.036%; halothane, 0.226 ± 0.015%, and methoxyflurane, 0.0469 ± 0.0135%), was added for exactly 2 h to the stream of N_2O delivered to the patients. These inspired concentrations resulted in a sum of alveolar concentrations equalling approximately 0.6 MAC. The average coefficient of variation of the measured inspired concentrations in all experiments for all anesthetics was 0.03. To minimize the second gas effect, the inspired concentration of N_2O was decreased by 5% (*i.e.*, to 60-65%) when the potent inhaled agents were introduced. When the potent inhaled agents were discontinued (*i.e.*, after 2 h), anesthesia was maintained for the remainder of the operation with thiopental, fentanyl, and 60-65% N_2O.

Samples of inspired (F_I), end-tidal (F_A), and mixed-expired (F_M) gases were taken during the 2-h washin period. F_I samples were collected proximal to the nonrebreathing valve. F_A samples were collected through a catheter, the tip of which was placed near the tracheal end of the endotracheal tube. The endotracheal tube was connected to the nonrebreathing valve with flexible Teflon[R] tubing whose internal volume was approximately 100 ml. Teflon[R] tubing was used to avoid the absorption and release of anesthetic that occur with plastics such as polyethylene, and the added 100 ml of dead space was used to prevent contamination of end-tidal samples with F_I. Expired gases

were conducted *via* a flexible Teflon[R] tube to an aluminum mixing chamber. F_M samples were collected distal to the aluminum mixing chamber. All gas samples were collected in 50 ml glass syringes that were stored upright (to produce a slight positive pressure) until analyzed.

F_A samples were taken during washin at 0.25 and 0.5 min after the start of administration of the potent agents in six patients and with each breath for the first 0.5 min in the other three patients. F_A samples were then collected at 0.75, 1, 1.5, 2, and 3 min. F_A, F_I, and F_M samples were collected at 5, 7, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, and 120 min. F_I samples were not collected during the first 3 min for logistical reasons. The F_I for the first 3 min was assumed to equal the average F_I for the 10, 15, and 20 min samples. Adequate F_M samples could not be obtained during the first 3 min because 1 min was required to ensure adequate washin of the mixing chamber. Values for F_M during the first 3 min were estimated by the following formula:

$$F_M = f_A \cdot F_A + f_D \cdot F_I$$

where f_A equals the fraction of ventilation coming from the alveoli and f_D equals the fraction of ventilation coming from the dead space. f_A and f_D are the average values calculated from the 10, 15, and 20 min samples using this same formula (*i.e.*, substitute 1 minus f_A for f_D and solve for f_A; and substitute 1 minus f_D for f_A and solve for f_D).

During washout (*i.e.*, after administration of the four anesthetics was discontinued), F_A and F_M gas samples were drawn at the same intervals as drawn during the 120 min of washin. In addition, F_A and F_M samples were drawn at approximately 150, 200, 350, 500, 700, 1,200, 1,800, and 2,700 min and then once a day for a total of 5 to 9 days. To ensure that the inspired concentration of the four anesthetics was zero, the delivery tubing was changed at the start of washout. Similarly, samples taken after the first 2 to 3 h of washout were collected in "fresh" glass syringes that had not been used to draw samples at the higher, anesthetizing concentrations. In addition, the nonrebreathing system used for anesthetic delivery was set aside and a "fresh" system was used in its place. The sampling protocol was interrupted during washout by the end of surgery and extubation. Gas samples were not collected after extubation until the patients were awake enough to be cooperative; they were then collected while the patient breathed through a mouthpiece and a low resistance nonrebreathing valve. Noseclips were used to prevent breathing through the nose. Minute ventilation was measured with a waterseal spirometer concurrently with the drawing of washin and washout samples.

To separate and detect isoflurane, enflurane, halothane, and methoxyflurane, we used a two-column gas chromatograph (Tracor® Model 550). Each column was composed of 10% SF 96® on Chromasorb WHP®, 68/

TABLE 1. Uptake and Metabolism of Anesthetics as Assessed by Mass Balance in Nine Patients Compared with the Results of Previous Mass Balance and Metabolite Recovery Studies

Anesthetic	Total Uptake (ml)	Total Recovery (ml)	Per Cent Recovery	Recovery Normalized to Isoflurane (%)	Normalized Metabolism (%)	Results of Previous Studies		
						Per Cent Recovery	Metabolites as a Per Cent of Total Uptake	References
Isoflurane	381 ± 25	354 ± 28	92.8 ± 4.0	100	0*	95	0.2	(7)
Enflurane	682 ± 43	579 ± 48	84.9 ± 3.8	91.5 ± 1.0	8.5 ± 1.0	85	2.4	(3)
						90–91		(10)
Halothane	356 ± 22	179 ± 13	50.2 ± 2.3	53.9 ± 0.9	46.1 ± 0.9	37	11–25	(6)
							17–20	(1)
						41–45		(10)
Methoxyflurane	127 ± 12	29 ± 2	23.1 ± 1.9	24.7 ± 1.6	75.3 ± 1.6	29–35	48	(2)

Values are mean ± SE.

* Metabolism of isoflurane was assumed to be 0 for this calculation.

80-mesh, 0.32 cm by 6.1 m. Nitrogen carrier was delivered at 45 ml/min through the column to a flame ionization detector at 200° C, which was supplied by hydrogen at 40 ml/min and air at 280 ml/min. One column was maintained at 30° C and was used to separate the isoflurane, enflurane, and halothane; retention times were 3, 3.5, and 5 min, respectively. The second column was kept at 65–70° C and was used to separate methoxyflurane from the other anesthetics. Results were recorded separately on a dual-channel strip recorder. Peak heights were proportional to concentration over the entire range of concentrations studied. Calibration standards prepared as described previously[9] were injected at intervals during each study.

To assess the total uptake of anesthetic and the total elimination of anesthetic by ventilation, uptake and elimination rates were calculated for each anesthetic at each time point. The uptake rates were calculated as: $\dot{V}_E \cdot (F_I - F_M)$, where $\dot{V}_E$ equals minute ventilation. The elimination rates were calculated as $\dot{V}_E \cdot F_M$. 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) was calculated by the same method, and the terminal recovery was estimated by multiplying the elimination rate at the final time point by the terminal time constant (determined separately for each anesthetic in each patient). The total recovery was divided by the total uptake, for each anesthetic, and multiplied by 100 to produce the per cent recovery (i.e., the percentage of anesthetic taken up that is eliminated by ventilation).

These mass balance data were then used to determine the extent of anesthetic metabolism. We assumed that isoflurane was not metabolized, and that the percentage recovery of isoflurane would not be 100% because of other sources of anesthetic loss (e.g., through the wound or skin and in the urine or feces). We also assumed that these other sources of anesthetic loss would decrease the

recovery of each anesthetic equally. To compensate for these losses, the percentage recovery of each anesthetic was normalized to that of isoflurane by dividing the percentage recovery for the anesthetic by the percentage recovery for isoflurane. Deficits in per cent normalized recovery were assumed to be due to metabolism (the per cent normalized metabolism).

Results

Estimates of the percentage of anesthetic metabolized and the per cent normalized metabolism differed considerably among the anesthetics (table 1). A minimal percentage of the enflurane was metabolized, whereas approximately one-half of the halothane and more than three-fourths of the methoxyflurane were metabolized.

Discussion

Our results indicate that a large percentage of some inhaled anesthetics is metabolized and therefore imply a considerable role for metabolism in the elimination of these anesthetics. In contrast, popular belief holds that the primary route of elimination of inhaled anesthetics is via ventilation. This is true for isoflurane and enflurane: analysis by mass balance indicates that ventilation clears 93% and 85%, respectively, of the total anesthetic taken up. However, for halothane, ventilation and the organs of metabolism (liver, kidney, and lungs[10,11]) are equally important, each being responsible for elimination of about one-half of the halothane taken up. For methoxyflurane, the organs of metabolism are most important, and elimination of methoxyflurane in exhaled gases may be unimportant.

These mass balance estimates for metabolism are 1.5 to 3 times greater than estimates determined by the recovery of metabolites (table 1). This difference is not surprising. Recovery of metabolites will underestimate the true rate of metabolism unless all metabolites can be recovered or accounted for, and complete recovery is un-
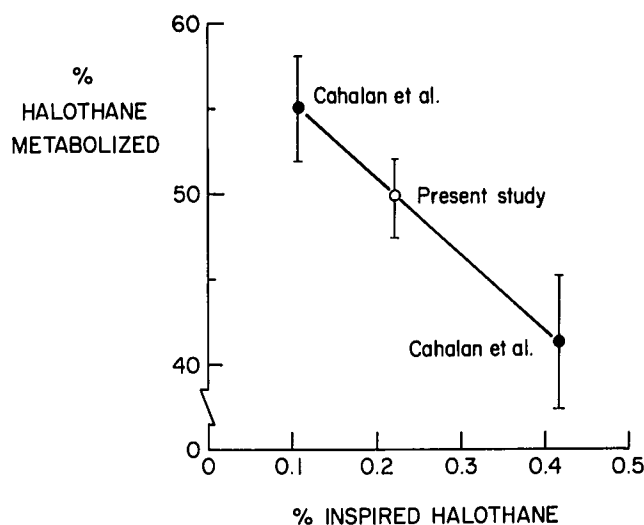
FIG. 1. Plot of the percentage of halothane metabolized against the inspired concentration, in humans. The value measured in this study is plotted with those determined by Cahalan *et al.*[9] Values are mean ± SE.

likely. Estimates based on mass balance studies are probably more accurate (particularly when normalized to the recovery of isoflurane).

Although our mass balance estimates for the per cent of anesthetic taken up that is metabolized are greater than those based on recovery of metabolites,[1-3,7] our estimates might be low for two reasons. First, we assumed that metabolism of isoflurane is inconsequential and, thus, that incomplete recovery of isoflurane can be attributed to losses common to all of the anesthetics (*i.e.*, through the wound or skin, or in urine or feces). This assumption results in an underestimate of metabolism of the other anesthetics by a factor equal to the percentage of isoflurane that is metabolized. This factor, however, appears to be inconsequential.[7,12]

Second, administration of one inhaled anesthetic with another anesthetic may inhibit the metabolism of the second anesthetic. Published reports suggest inhibition of enflurane metabolism by halothane[13] and inhibition of halothane metabolism by isoflurane.[14] If these reports from animal studies apply to our results for humans, then we have underestimated the total metabolism of enflurane and halothane.

However, our data suggest that co-administration of inhaled anesthetics does not inhibit the metabolism of inhaled anesthetics in humans. The similarity of our per cent recoveries to those of previous mass balance studies in which only a single anesthetic was administered (table 1) argues against inhibition of metabolism due to the simultaneous administration of the four anesthetics. Direct comparison of our results with results from other studies is limited, however, because both the duration of anes-

thetic administration and the inspired concentration may affect the percentage of anesthetic metabolized. One study that can be directly compared is a previous study from our group that was similar in design.[9] In that study two anesthetics, halothane and enflurane, were administered simultaneously at two different concentrations for exactly 2 h, and the percentage of anesthetic metabolized was assessed by mass balance. Comparison of our present results with the results of this previous study (fig. 1) reveals a linear relationship, despite the fact that in the present study we administered four anesthetics simultaneously. This relationship supports our conclusion that co-administration does not appreciably interfere with metabolism. Therefore, our results probably do not appreciably underestimate the magnitude of metabolism that would occur with administration of a single agent.

Our observations contrast with those of Fish and Rice[13] and Fiserova-Bergerova,[14] who reported inhibition of the metabolism of one anesthetic by another in rats. The reasons for these differences are not clear. Perhaps metabolism is less affected by concurrent administration in humans than in rats, or perhaps we did not find an inhibitory effect on metabolism because most metabolism took place during recovery from anesthesia, when concentrations may be below those producing significant inhibition.

Our estimates for the percentages of anesthetic taken up that are metabolized may be greater than those that would be found at higher inspired concentrations. Because we administered all four potent inhaled anesthetics simultaneously, the inspired concentration of the individual anesthetics had to be reduced. Inspired concentration can be an important determinant of the fraction of anesthetic metabolized (as demonstrated in fig. 1). The accepted explanation for this phenomenon is that metabolism is limited at higher concentrations by saturation of the enzymes responsible for metabolism.[6,10,12,15,16] If the percentage metabolized is less at inspired concentrations that are higher than those we used, our results would overestimate anesthetic metabolism for a typical anesthetizing concentration.

Methoxyflurane undergoes more metabolism than do other anesthetics. The reasons for this greater metabolism are not clear. Some investigators have speculated that this high rate of metabolism in part is the result of methoxyflurane's high solubility in blood (relative to the other inhaled anesthetics).[2] These investigators suggest that the high blood solubility limits elimination into alveolar gas, and the methoxyflurane molecules consequently recirculate through the organs of metabolism many times before they can be eliminated in exhaled gases. This explanation implies that the alveolar partial pressure of methoxyflurane is sustained during recovery at a higher level than the alveolar partial pressure of other, less soluble anesthetics. However, we have found that the alveolar

partial pressure of methoxyflurane is not sustained; it decreases at nearly the same rate as enflurane.[17] Thus, methoxyflurane's high solubility does not result in a sustained partial pressure and, therefore, a slow decline in the partial pressure is not the cause of the increased metabolism. Rather, methoxyflurane is metabolized so rapidly that the decline in methoxyflurane's alveolar partial pressure is accelerated.

The validity of using isoflurane as a control for the losses of anesthetics through the skin, in urine, and across the wound may be questioned. Losses through skin and in urine are minimal, regardless of the anesthetic.[6,8] Loss through the wound will depend on the distribution to the tissues that are exposed and on the tissue/gas partition coefficients.[18-20] Distribution to the tissues will be comparable for the anesthetics because of the identity of blood flows to tissue and because of the similarity of blood/tissue partition coefficients.[18] However, tissue/gas partition coefficients differ among anesthetics by an order of magnitude.[18] The smaller the tissue/gas partition coefficient, the greater the loss from an open wound (or skin) to the surrounding air. Thus, the rate of loss of isoflurane from the wound should exceed the rate for other, more soluble anesthetics, and normalization of the data for enflurane, halothane, and methoxyflurane to the data for isoflurane will cause an underestimate of the metabolism of enflurane, halothane, and methoxyflurane. However, because 93% of the isoflurane was recovered, this underestimate cannot be large.

In summary, we have found the per cent metabolism of enflurane, halothane, and methoxyflurane (when measured by mass balance) to be greater than previously reported for studies that recovered metabolites. The implication of these results is that elimination of anesthetics *via* metabolism can be a major factor in the total elimination of anesthetic from the body.

Isoflurane (Forane[R]) and enflurane (Ethrane[R]) for this study were donated by Anaquest. Halothane (Fluothane[R]) was donated by Ayerst Laboratories.

References

1. Rehder K, Forbes J, Alter H, Hessler O, Stier A: Halothane biotransformation in man: A quantitative study. ANESTHESIOLOGY 28:711–715, 1967

2. Holaday DA, Rudofsky S, Treuhaft PS: The metabolic degradation of methoxyflurane in man. ANESTHESIOLOGY 33:579–593, 1970

3. Chase RE, Holaday DA, Fiserova-Bergerova V, Saidman LJ, Mack FE: The biotransformation of Ethrane in man. ANESTHESIOLOGY 35:262–267, 1971

4. Hitt BA, Mazze RI, Cousins MJ, Edmunds HN, Barr GA, Trudell JR: Metabolism of isoflurane in Fischer 344 rats and man. ANESTHESIOLOGY 40:62–67, 1974

5. Fiserova-Bergerova V: Changes in fluoride content in bone. ANESTHESIOLOGY 38:345–351, 1973

6. Cascorbi HF, Blake DA, Helrich M: Differences in the biotransformation of halothane in man. ANESTHESIOLOGY 32:119–123, 1970

7. Holaday DA, Fiserova-Bergerova V, Latto IP, Zumbiel MA: Resistance of isoflurane to biotransformation in man. ANESTHESIOLOGY 43:325–332, 1975

8. Stoelting RK, Eger EI II: Percutaneous loss of nitrous oxide, cyclopropane, ether and halothane in man. ANESTHESIOLOGY 30:278–283, 1969

9. Cahalan MK, Johnson BH, Eger EI II: Relationship of concentrations of halothane and enflurane to their metabolism and elimination in man. ANESTHESIOLOGY 54:3–8, 1981

10. Van Dyke RA, Chenowith MB: The metabolism of volatile anesthetics. II. *In vitro* metabolism of methoxyflurane and halothane in rat liver slices and cell fractions. Biochem Pharmacol 14:603–609, 1965

11. Blitt CD, Gandolfi AJ, Soltis JJ, Brown BR Jr: Extrahepatic biotransformation of halothane and enflurane. Anesth Analg 60:129–132, 1981

12. Halsey MJ, Sawyer DC, Eger EI II, Bahlman SH, Impelman DMK: Hepatic metabolism of halothane, methoxyflurane, cyclopropane, Ethrane, and Forane in miniature swine. ANESTHESIOLOGY 35:43–47, 1971

13. Fish KJ, Rice SA: Halothane inhibits metabolism of enflurane in Fischer 344 rats. ANESTHESIOLOGY 59:417–420, 1983

14. Fiserova-Bergerova V: Inhibitory effect of isoflurane upon oxidative metabolism of halothane. Anesth Analg 63:399–404, 1984

15. Sawyer DC, Eger EI II, Bahlman SH, Cullen BF, Impelman D: Concentration dependence of hepatic halothane metabolism. ANESTHESIOLOGY 34:230–234, 1971

16. Hitt BA, Mazze RI, Beppu WJ, Stevens WC, Eger EI: Enflurane metabolism in rats and man. J Pharmacol Exp Ther 203:193–202, 1977

17. Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB: Pharmacokinetics of inhaled anesthetics in humans: Measurements during and after the simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane, and nitrous oxide. Anesth Analg 65:575–582, 1986

18. Eger EI II: Anesthetic Uptake and Action. Baltimore/London, Williams & Wilkins, 1981, pp 82–93

19. Severinghaus JW: The rate of uptake of nitrous oxide in man. J Clin Invest 33:1183–1189, 1954

20. Severinghaus JW: Uptake and Distribution of Anesthetic Agents. New York, McGraw-Hill, 1963, p 70