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Percutaneous Loss of Desflurane, Isoflurane, and Halothane in Humans

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We studied the percutaneous losses of the new inhaled anesthetic, desflurane (I-653), and of isoflurane and halothane during anesthetic administration and elimination in seven healthy male volunteers. Anesthesia was induced and maintained with midazolam, thiopental, and fentanyl. We administered 70% N_2O for 30 min, and then administered 2% desflurane, 0.4% isoflurane, and 0.2% halothane concurrently with 65% N_2O for 30 min. Inspired, end-tidal, and mixed-expired gas samples were collected during administration of the volatile agents and for 5–7 days of elimination. The right arm and hand of each subject was enclosed in a sealed glass cylinder having a port at each end, one for sampling and both for flushing with N_2 after anesthetic administration and every 15 min thereafter. We sampled gases from the cylinder during administration and for the 150 min of elimination and analyzed their anesthetic concentrations by gas chromatography. The surface area of the enclosed portion of the arm was measured, and the total body surface area was calculated. All values were normalized to (*i.e.*, divided by) the end-tidal (alveolar) concentration at the end of administration. During administration, percutaneous loss of halothane was 3.5 times that of desflurane and 2 times that of isoflurane. During elimination, the loss of halothane was 6 times and 2 times greater than the loss of desflurane and isoflurane, respectively. Percutaneous loss of halothane significantly exceeded that of isoflurane. The elimination values included an estimate of elimination after 150 min. The percutaneous loss of each anesthetic was 2- to 3-fold greater during elimination than administration. Although the total (administration and elimination) values for percutaneous loss were several times greater than suggested by previous reports, they represent a minimal fraction of the total anesthetic taken up *via* the lungs. (Key words: Anesthetics, volatile: desflurane; isoflurane; halothane. Pharmacokinetics. Skin: percutaneous anesthetic loss.)

RESULTS from a previous study suggest that the percutaneous loss of ether and halothane at constant alveolar (end-tidal) concentrations represents a trivial fraction of the total uptake of either agent.[1] However, the percutaneous loss of anesthetic during elimination was not included in these calculations. If percutaneous loss during recovery from anesthesia is appreciable, then percutaneous loss may constitute an appreciable fraction of uptake. If this is true, studies of kinetics and studies of metabolism based on mass balance calculations might be vitiated. We hypothesized that percutaneous loss of anesthetic would be larger during anesthetic elimination than during administration but that even this greater loss would not materially affect calculations of metabolism or kinetics. Further, we hypothesized that potent agents of high lipid solubility or high blood solubility would diffuse through the skin more rapidly than would agents of lower solubilities. To test both hypotheses, we measured the percutaneous loss of isoflurane and of a new volatile agent, desflurane (I-653) and reevaluated the percutaneous loss of halothane by comparison to the results for these agents.

Materials and Methods

With approval from the University of California San Francisco Committee on Human Research and informed consent from each subject, we studied seven healthy ASA physical status 1 male volunteers (age 24.8 ± 5.0, body weight 74.5 ± 6.8 kg, and height 179 ± 4.6 cm [mean ± SD]). No surgical procedures were done before or after the study.

Anesthesia was induced intravenously with midazolam (4–6 mg) and/or fentanyl (0.2–0.4 mg) and thiopental (200–500 mg). Vecuronium 10 mg was administered to facilitate intubation of the trachea and control of ventilation. These drugs also were given as needed throughout the period of anesthesia. Ventilation was adjusted to provide an end-tidal CO_2 tension ($P_{ET}CO_2$) of 35–40 mmHg (measured by infrared analysis, Datex 254 analyzer). Blood pressure, ECG, esophageal temperature, and O_2 saturation were monitored.

Each subject's right arm was enclosed in a glass cylinder 50 cm in length and 12.5 cm in internal diameter, the distal end of which was sealed with glass. The proximal end was sealed with Mylar® film, which was taped to the volunteer's arm and the glass cylinder with 3M Steri-Drape® to make an airtight seal. Mylar was chosen because of the very low solubility of anesthetics in this plastic.[2] Thus, neither it nor the glass would confound the results; that is, neither would absorb anesthetic that had moved through the skin to the enclosed space. (The Steri-Drape

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was applied *outside* of the Mylar). The absence of a leak in the system was confirmed by pressurizing it with 100% N_2. The glass cylinder had two ports, one for sampling and one for flushing the cylinder with N_2. The system was flushed with 100% N_2 8 l/min, for the 2 min preceding administration of the volatile anesthetics, for the period immediately before discontinuing them, and every 15 min thereafter for the first 150 min of elimination. This schedule of flushing restricted the partial pressure of anesthetic in the gas space surrounding the arm to a partial pressure that did not limit diffusion from the epidermis.

The volatile inhaled anesthetic agents, N_2O, and O_2 were delivered to the subject *via* a nonrebreathing circuit. Administration of 70% N_2O for 30 min was followed by delivery of a mixture of 2% desflurane, 0.4% isoflurane, and 0.2% halothane in 65% N_2O/balance O_2 for a period of 30 min. After 30 min, administration of the volatile agents was discontinued. Anesthesia was maintained with 65% N_2O and intravenous agents, and paralysis with vecuronium was maintained for an additional 150 min, after which each subject was allowed to awaken.

From the glass cylinder encasing the subject's arm, we drew gas samples into 50-ml glass syringes at the following times: just prior to administration of the volatile anesthetics and at 10, 15, 20, 25, and 28 min during the period of administration. During the first 29 min of elimination, gas samples were collected every 5 min. From 30 to 150 min of elimination, samples were collected at 15-min intervals, with a 2-min period of flushing with N_2 separating these intervals. Within each interval, samples were obtained at 0, 6–7, and 13 min. Mixing of the volatile agents was ensured by repeatedly injecting and withdrawing with the sampling glass syringe before drawing each sample. The glass cylinder was removed before extubation of the trachea.

We calculated the total percutaneous loss of the three volatile anesthetics during each sampling interval within the 30-min administration and the 150-min elimination periods as:

$$\text{percutaneous loss} = V \cdot \Delta \cdot TSA \cdot ASA^{-1}$$

where V is the volume of the gas within the glass chamber; TSA is the total body surface area; ASA is the enclosed arm surface area; and Δ is the difference in concentration for the interval of measurement. The volume of the gas surrounding the arm within the glass chamber was measured by displacement. The total body surface area was estimated from the subject's height and weight.[3] The enclosed arm surface area was measured by applying a single layer of aluminum foil to the exposed surface of the arm, weighing it, and multiplying this weight by the area (square centimeters) per gram aluminum (measured separately for the specific foil used). Note that the calculation of total percutaneous loss assumes that the loss from other cutaneous surfaces is the same as the loss we measured from the arm—an assumption that may not be precisely correct because of differences in surrounding clothing, skin thickness, or cutaneous blood flow.

We collected and analyzed samples of the end-tidal (F_A), mixed expired (F_M) and inspired (F_I) gas during the 30 min of anesthetic administration, during the 150 min of elimination of the three volatile agents, and for the next 5–7 days.[4] We measured ventilation ($\dot{V}_E$) by spirometry. As will be shown, the percutaneous rate of loss of the three anesthetics during the first 150 min of elimination correlated with the F_A (alveolar concentration) of anesthetic. Accordingly, the percutaneous loss of anesthetics after the first 150 min of elimination was estimated from the continuing decay in F_A.

The concentration of each anesthetic in each sample was determined by gas chromatography. A Gow-Mac® Series 580 gas chromatograph with a column composed of 10% SF-96 on Chromasorb WHP, 68/80-mesh, 0.32 cm × 6.1 m maintained at 48° C was used. A carrier stream flowing at 15 $ml \cdot min^{-1}$ was delivered through the column to a flame ionization detector at 150° C, supplied by H_2 at 20 $ml \cdot min^{-1}$ and by air at 200 $ml \cdot min^{-1}$. Calibration (tank) standards were injected at intervals during each study. Peak heights were proportional to the concentration over the entire range of the concentrations studied.

We calculated uptake of anesthetic (reported separately)[4] at each point in time as $V_E(F_I - F_M)$. Elimination at each point in time was calculated as $V_E \cdot F_M$.

Data Analysis

The total percutaneous losses of the three anesthetics during anesthetic administration and elimination were analyzed by analysis of variance. Differences between anesthetics were evaluated with paired *t* tests with Bonferroni corrections where appropriate. Total percutaneous losses of each anesthetic during administration were compared with losses during elimination using a paired *t* test. For the paired *t* tests applying Bonferroni correction, we accepted a value of $P \leq 0.0166$ as significant. All comparisons were made after percutaneous anesthetic losses were normalized to (*i.e.*, divided by) the F_{A0} value (*i.e.*, the last F_A during administration of anesthetic: approximately 0.12% halothane, 0.29% isoflurane, and 1.8% desflurane). We plotted the rate of percutaneous loss normalized to F_{A0} during administration. We also plotted the rate of percutaneous loss during elimination after normalizing it to both F_{A0} to F_{A-10} (the F_A obtained 10 min before the start of a sampling period).

TABLE 1. Percutaneous Losses of Desflurane, Isoflurane, and Halothane

Percutaneous Loss	Desflurane	Isoflurane	Halothane
Durating 30-min administration			
Vapor loss (ml)	0.216 ± 0.122	0.070 ± 0.041	0.051 ± 0.028
Loss (ml · F_{A0}^{-1})	0.147 ± 0.084	0.275 ± 0.161	0.504 ± 0.282
During elimination			
Vapor loss (ml)	0.444 ± 0.171	0.244 ± 0.090	0.200 ± 0.042
Loss (ml · F_{A0}^{-1})	0.272 ± 0.094	0.880 ± 0.272	1.772 ± 0.432
Total anesthetic uptake (ml)	467 ± 128	162 ± 46	113 ± 12
Percutaneous loss (% of anesthetic uptake)	0.157 ± 0.041	0.196 ± 0.037	0.228 ± 0.034

Values are expressed as means ± SD.
For each anesthetic, loss during elimination was greater than during administration ($P < 0.01$). During administration, loss of halothane exceeded that of isoflurane or desflurane ($P < 0.005$). During elimination, loss of halothane exceeded that of isoflurane and desflurane and loss of isoflurane exceeded that of desflurane ($P < 0.001$).

Results

For technical reasons, the isoflurane data were obtained from six instead of seven subjects. During administration, total percutaneous losses differed significantly among the three anesthetics (F = 5.98; $P = 0.025$) (table 1 and figs. 1–3). Percutaneous losses were significantly greater for halothane than for desflurane ($P = 0.0034$) and isoflurane ($P = 0.0005$). Total loss of isoflurane during administration, did not differ significantly from that of desflurane. The loss of anesthetic was inconsequential (<0.001 ml vapor) during the first 10 min of administration of volatile anesthetics but increased thereafter, and appeared to approach a plateau at 25–30 min (fig. 1).

During elimination, the percutaneous losses normalized for F_{A0} differed significantly among anesthetics (F = 29.50; $P < 0.005$). Loss for each anesthetic differed among the three; it was greatest for halothane, intermediate for isoflurane, and least for desflurane ($P = 0.001$ for desflurane *vs.* isoflurane; $P < 0.0001$ for desflurane *vs.* halothane; and $P = 0.0003$ for isoflurane *vs.* halothane) (table 1 and fig. 2). For each anesthetic, loss was significantly greater during elimination than during administration ($P = 0.0064$, $P = 0.001$, and $P = 0.0002$ for desflurane, isoflurane, and halothane, respectively).

Changes in the rates of percutaneous loss during elimination paralleled the decay of F_A during elimination (fig. 2). When the rates of percutaneous losses of each anesthetic during elimination were normalized to F_{A-10} (the F_A obtained 10 min before the start of a sampling period), the losses for each anesthetic reached a plateau after 30 min (fig. 3). These data may be interpreted as percutaneous clearance.

Discussion

As we hypothesized, the percutaneous losses of the three anesthetics during elimination were 2- to 4-fold

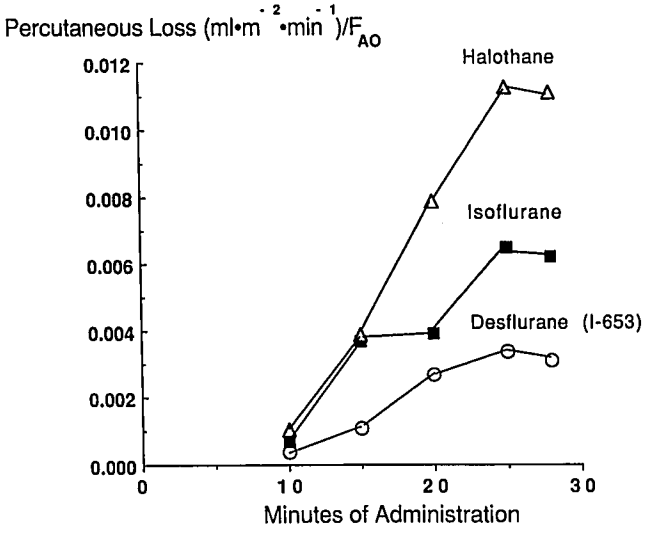

FIG. 1. The rate of percutaneous loss (milliliters per minute per square meter) of the three anesthetics during administration, normalized for their F_{A0}, is greatest for halothane, intermediate for isoflurane, and least for desflurane.

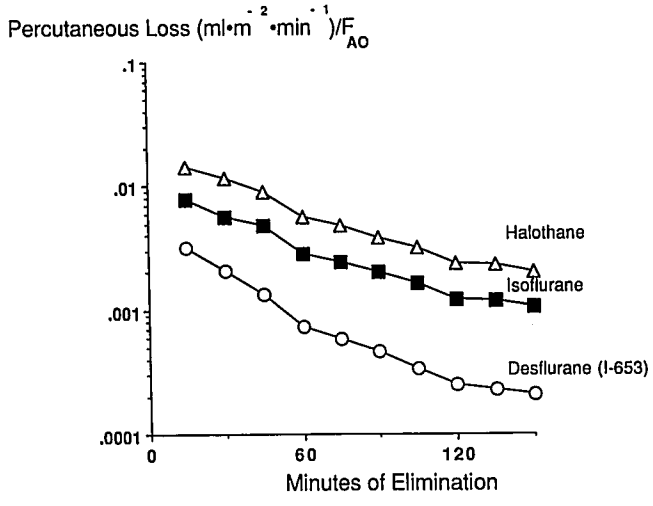

FIG. 2. The rate of percutaneous loss (milliliters per minute per square meter) of the three anesthetics during elimination, normalized for their F_{A0}, is greatest for halothane, intermediate for isoflurane, and least for desflurane.

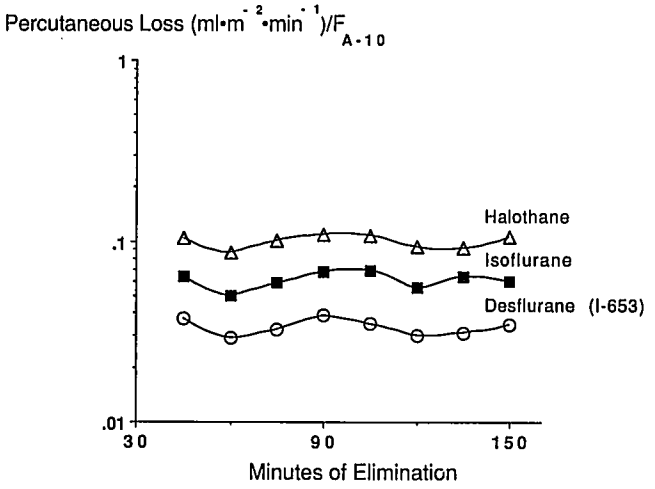

FIG. 3. The rate of percutaneous loss (milliliters per minute per square meter) of the three anesthetics during elimination, normalized for their F_{A-10}, is greatest for halothane, intermediate for isoflurane, and least for desflurane. We estimated loss after 150 min of elimination from the constant relationship of loss to F_{A-10} indicated in figure 3 and from our measurements of F_A over the ensuing several days. We chose F_{A-10} because of the 10-min transit time suggested by the data given in figure 1, and because of the constancy of the ratio of the loss to F_{A-10}. The use of other F_A values, such as the F_A at the start of a collection period, did not give a constant ratio.

higher than losses during administration (table 1). This result would be modified by the duration of anesthesia: a longer duration would increase the loss during administration more than during elimination. Prolonged anesthesia would result in a greater loss during rather than after anesthetic administration. However, in our study (and, we predict, in a study that imposes an anesthetic administration of considerably greater duration), the total loss was too small to affect kinetics or metabolic studies based on mass balance. Finally, as predicted, the rate of percutaneous loss was a direct function of anesthetic solubility in blood or fat. Our finding of a good correlation between the rate of percutaneous loss and anesthetic solubility is in conflict with the lack of correlation previously reported by others in an *in vitro* investigation, perhaps because those workers studied anesthetics having widely differing molecular weights.[5] Diffusion is slower with larger molecules.

The rate of loss of halothane at the end of 30 min of administration ($0.0110\ ml \cdot min^{-1} \cdot m^{-2} \cdot F_{A0}^{-1}$) was similar to that previously reported for halothane delivered for a far longer time at constant F_A (alveolar concentration) ($0.0084\ ml \cdot min^{-1} \cdot m^{-2} \cdot F_A^{-1}$).[1] The similarity of these values suggests that a steady state was approached within 30 min. A steady state clearly was not present early in administration: figure 1 reveals that 10 min is required to raise the subcutaneous levels of anesthetic to partial pressures sufficient to traverse the skin. Included in this is the time needed to traverse the skin.

We did not measure percutaneous loss after 150 min of elimination. We estimated loss after this time from the constant relationship of loss to F_{A-10} indicated in Figure 3 and from our measurements of F_A over the next 5–7 days. We chose F_{A-10} because of the 10-min transit time suggested by the data shown in fig. 1 and because of the constancy of the ratio of the loss to F_{A-10} indicated in figure 3. (The use of other F_A values, such as the F_A at the start of a sampling period, did not provide a constant ratio.) The graphs in figure 3 are flat, as they should be if they represent clearance, since such clearance should be a first-order phenomenon, proportional to the partial pressure of anesthetic in the skin.

Since the same cutaneous blood flow applies to the three anesthetic agents, different diffusion and solvent characteristics must be invoked to explain their differences in percutaneous losses. Results of a previous study suggest that diffusion limits percutaneous loss.[5] A difference in molecular weight could alter diffusion characteristics and result in different rates of percutaneous loss. However, desflurane, isoflurane, and halothane have similar molecular weights. Thus, the difference in diffusion likely is due to a difference in the solvent characteristics of the skin.

If diffusion from the dermal layer to subcutaneous adipose tissue could decrease the dermal anesthetic partial pressure,[6] it also should decrease the percutaneous loss of anesthetic. This intertissue diffusion might be expected to have a greater effect on anesthetics with a greater lipid solubility, such as halothane.[7] That is, the greater lipid solubility might provide a greater sink that would draw halothane from the dermis. If so, halothane should have had the smallest, and not the greatest, percutaneous loss of the agents we studied. Perhaps the differences in fat solubility are too small to affect loss. Alternatively, the reservoir provided by fat may be so large that it effectively constitutes an infinite sink for all anesthetics and thus does not discriminate among anesthetics.

We measured percutaneous anesthetic losses *via* the skin of the forarm and hand, a limited surface area. Cutaneous blood flow varies considerably among different skin sites,[8] as does the thickness of the epidermis. These regional variations are likely to affect the anesthetic percutaneous losses from different portions of the body surface. Similarly, local differences in blood flow, as would be obtained by warming or cooling the skin, are expected to change percutaneous losses proportionately.[1] By increasing blood flow, anesthetics may increase their percutaneous transfer. Thus, our calculations of total percutaneous loss should be considered to be estimates rather than precise values. However, the relative rates of per-

cutaneous loss for the three anesthetics are probably well represented by our data.

In summary, for the relatively brief anesthetic exposure, applied in the current study, the rates of the percutaneous losses of desflurane, isoflurane, and halothane were greater during elimination than during administration. In addition, the rates of loss correlated with anesthetic solubility in blood, and did not comprise an appreciable proportion of the total anesthetic uptake. Therefore, percutaneous loss probably affects neither kinetic characteristics nor metabolic studies based on mass balance.

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