Percutaneous Loss of Nitrous Oxide, Cyclopropane, Ether and Halothane in Man

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Percutaneous losses of nitrous oxide, cyclopropane, ether and halothane were determined in patients undergoing elective surgical procedures. After 100 minutes of anesthesia, the percutaneous loss of nitrous oxide was 3.6 ml/min/m² at an average alveolar concentration of 70 per cent, and cyclopropane loss was 0.22 ml/min/m² at an average alveolar concentration of 15 per cent. After 60 minutes of anesthesia, halothane loss at an alveolar concentration of 0.9 per cent was 0.0076 ml/min/m². Ether loss after 60 minutes at an alveolar concentration of 4 per cent was 0.15 ml/min/m². These losses represent only a small fraction of anesthetic uptake after 60–100 minutes of anesthesia; the largest fraction of total uptake, 6.4 per cent, was obtained with nitrous oxide. Percutaneous loss of nitrous oxide increased in a rectilinear manner, with a fivefold increase as skin temperature rose from 20 to 40 C. Our data suggest diffusion is more important than cutaneous blood flow in limiting loss of anesthetic through the skin.

Loss of an inert gas through the skin prevents total body equilibration with that gas. The amounts, significances and time courses of percutaneous losses of anesthetic agents have not been evaluated fully. Waters and Orcutt, in 1933, reported nitrous oxide loss through the skin to be about 230 ml/hr/m² in two patients after 50 and 80 minutes.[1] In this study we report the percutaneous losses of nitrous oxide, cyclopropane, ether and halothan (Fluothane®) at constant alveolar anesthetic partial pressures. We also report the effects of variations in skin temperature on the magnitude of percutaneous nitrous oxide loss.

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Method

Nitrous oxide loss was studied in eight patients at a constant inspired (equal to alveolar) concentration of 70 per cent by maintaining inspired O_2 at 30 per cent as determined by a Beckman–Pauling oxygen analyzer. Cyclopropane, ether and halothane were studied at constant alveolar concentrations following the induction period. End-tidal gas samples were analyzed by an infrared analyzer or gas chromatograph and the inspired concentrations adjusted to maintain alveolar cyclopropane concentration at 15 per cent (four patients) or 20 per cent (three patients); alveolar ether concentration at four per cent (five patients); alveolar halothane concentration at 0.9 per cent (six patients). All patients were studied during elective surgical procedures except three subjects (volunteers) who received 20 per cent cyclopropane without surgery. Percutaneous losses in these three subjects were studied for one hour after at least five hours of anesthesia. All nitrous oxide anesthetics were supplemented with halothane except in one patient who received intravenous meperidine (Demerol®). Inspired gases in other studies were the anesthetic and O_2. Thiopental and muscle relaxants were used as necessary except in the three subjects who received 20 per cent cyclopropane. The tracheas of all subjects were intubated for the duration of the study.

The effects of variation in skin temperature on percutaneous losses of nitrous oxide were determined in six additional patients. The studies were begun after 120 minutes of nitrous oxide anesthesia. Chamber and skin temperatures were varied by applying ice or heating pads to the outside of the chamber. Skin temperature was held stable at each temperature for at least 30 minutes. Percutaneous

loss rates are corrected to 0 C. Loss rates for all other studies are at room temperature (22–24 C).

A glass chamber 70 cm in length and 14 cm in diameter was placed over the hand, forearm and part of the arm. The distal end of the chamber was sealed with glass. The proximal open end was covered with a Mylar® plastic shield individually cut to fit the arm. A rubber dam covered this and was used to obtain an airtight seal about the forearm. Care was taken not to compress the vascular supply to the arm. The chamber was provided with four ports. Two were used for the placement of temperature probes. One probe was taped to the forearm and the other measured the gas temperature within the chamber. Except for the temperature-effect studies no attempt was made to control the temperature. Skin and ambient temperatures increased 1–2 C with all agents during the first 10–20 minutes following application of the chamber, and then remained constant for the duration of the study (skin temperatures 30.5–33.5 C; ambient temperatures 23.7–26.3 C). In two patients measurements of the opposite arm covered only with surgical drapes showed skin temperatures within 0.5 degrees of the enclosed areas, suggesting that the 1–2 C temperature increase noted above was related more to vasodilatation from anesthesia than to enclosure by the glass chamber. In the nitrous oxide studies the remaining two ports were connected to a pump which circulated the atmosphere about the enclosed arm. The pump was not used with the other studies because of both the explosion hazard with ether and cyclopropane and the possible loss of the agent to the rubber components of the pump. With these agents, mixing was assured by barbotage with a 100-ml syringe prior to each sample.

Prior to each nitrous oxide study the entire system was flushed with pure O_2. The oxygen concentration within the chamber was measured with a Beckman-Pauling meter. No silica gel absorbent was used, and the analyzed gases were returned to the chamber. The absence of a leak in the system was confirmed

TABLE 1. Average Percutaneous Loss/min/m² with Standard Deviation for Each Agent at the Alveolar Concentration at Which It Was Studied (F_A)*

Minutes of Anesthesia	Nitrous Oxide (8 Patients) F_A = 70 per cent		Cyclopropane (4 Patients) F_A = 15 per cent		Cyclopropane (3 Patients after 5 Hours of Anesthesia) F_A = 20 per cent		Ether (5 Patients) F_A = 4 per cent		Halothane (6 Patients) F_A = 0.90 per cent	
	ml/min/m²	SD	ml/min/m²	SD	ml/min/m²	SD	ml/min/m²	SD	ml/min/m²	SD
0	0		0		0		0		0	
10	0		0.069	0.047	0.283	0.009	0		0.0015	0.0016
20	0.67	0.96	0.152	0.100	0.341	0.057	0.010	0.014	0.0027	0.0023
30	2.41	0.88	0.141	0.033	0.326	0.041	0.042	0.039	0.0049	0.0024
40	2.17	0.90	0.170	0.098	0.334	0.064	0.051	0.013	0.0038	0.0011
50	2.39	0.86	0.162	0.094	0.295	0.088	0.109	0.058	0.0041	0.0023
60	2.51	0.72	0.153	0.045	0.322	0.057	0.161	0.290	0.0056	0.0025
70	2.99	0.78	0.152	0.071			0.174	0.216	0.0073	0.0052
80	3.04	0.68	0.170	0.051			0.149	0.152	0.0055	0.0019
90	3.04	1.19	0.230	0.114			0.202	0.316	0.0085	0.0024
100	2.91	0.68	0.210	0.180			0.094	0.065	0.0088	0.0047
110	3.54	0.95	0.260	0.167			0.129	0.042	0.0079	0.0040
120	3.67	0.95	0.221	0.094					0.0077	0.0012
130	3.71	0.79	0.270	0.175					0.0072	0.0027
140	3.82	1.25	0.180	0.093						
150	3.58	1.13	0.210	0.058						
160	3.62	1.06	0.240	0.141						
170	3.68	0.71	0.183	0.079						
180	2.94	0.95	0 200	0.048						

* All studies began with induction of anesthesia except the three cyclopropane experiments which were carried out for 60 minutes after at least five hours of cyclopropane–O_2 anesthesia.

by maintenance of a constant oxygen percentage. No method of leak detection was used with the other agents studied.

Ten-ml gas samples were drawn from the chamber into glycerinized glass syringes at the start of anesthesia and every ten minutes thereafter. All samples were analyzed by gas chromatography immediately after completion of the study. (We had determined previously that there was no loss of agent from the glycerinized syringes for the time period involved.) Nitrous oxide concentration was determined by a thermoconductivity detector after passage through KOH, Drierite®, and a 36 × ⅛-inch column of 40/60-mesh silica gel at 40 C. Cyclopropane and halothane concentrations were analyzed by a hydrogen flame detector after passage through 6 × ⅛-inch columns of 40/60-mesh silica gel at 90 and 150 C, respectively. Ether concentrations were determined with a 5 × ⅛-inch column of hexadecane on Chromosorb-P® at 40 C, using the flame detector.

The surface area of the enclosed arm was measured directly. The gas volume of the chamber with the arm in position was determined by water displacement. From this information we calculated ml anesthetic lost percutaneously per square meter of body surface area. Dividing this value by the per cent alveolar concentration gave ml/min/m² lost percutaneously per 1 per cent alveolar concentration.

Results

Table 1 summarizes the rates of loss of the four anesthetics. Table 2 shows the loss of each agent after it had reached a plateau. Row 2 shows the average skin loss/min/m² and standard deviation at the alveolar concentration studied (row 1). Nitrous oxide showed the greatest loss, 3.6 ml/min/m², which, converted to an hourly loss, amounts to 214 ml/m². This compares closely with the figure of 230 ml/hr/m² reported by Orcutt

TABLE 2. Characteristics of Percutaneous Losses of Anesthetics at Plateau Levels

	Nitrous Oxide	Cyclopropane	Ether	Halothane
1. Alveolar per cent	70	15	4	0.9
2. Ml percutaneous loss/min/m²*	3.57 ± 0.97	0.22 ± 0.11	0.15 ± 0.16	0.0076 ± 0.0031
3. Blood/gas partition coefficient[10]	0.47	0.42	12.1	2.3
4. Fat/blood partition coefficient**	2.2	16.2	3.8	60
5. Ml anesthetic carried in 150 ml blood***	49.4	13.9	72.6	3.1
6. Per cent of (5) lost through the skin (*i.e.*: (2)/(5) × 100)	7.2	1.6	0.21	0.25
7. Ml percutaneous loss/min/1.8 m²*	6.43	0.40	0.27	0.014
8. Calculated total body uptake (ml/min)*†	100[4]	16[7]	300[8]	13[9]
9. Per cent percutaneous loss/uptake* (*i.e.*: (7)/(8) × 100)	6.43	2.5	0.09	0.10
10. Ml percutaneous loss/min/m² at 1 per cent alveolar concentration (7.6 mm Hg)	0.051	0.015	0.038	0.0084
11. Per cent of nitrous oxide percutaneous loss at 1 per cent alveolar concentration	100	29.4	74.5	16.5

* After 60 (ether and halothane) or 100 (nitrous oxide and cyclopropane) minutes of anesthesia.

** Calculated as oil/gas partition coefficient times 0.6 + water/gas partition coefficient times 0.4 divided by blood/gas partition coefficient.

*** Calculated as alveolar per cent times 150 ml/min times the blood/gas partition coefficient.

† Adjusted to the alveolar per cent listed in row 1.

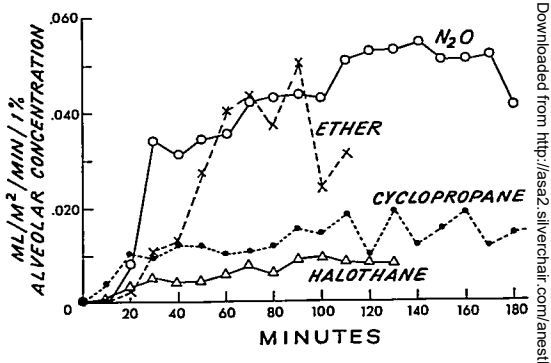

FIG. 1. Percutaneous loss/m²/min/1 per cent alveolar concentration plotted against the duration of anesthesia.

and Waters.[1] In four patients cyclopropane loss averaged 0.22 ml/min/m². In three additional patients studied after at least five hours of cyclopropane anesthesia ($F_A = 20$ per cent), the average percutaneous loss was 0.32 ml/min/m² (corrected to $F_A = 15$ per cent, 0.24 ml/min/m²). The amount of anesthetic in the blood flowing to each m² of skin was determined by assuming a cutaneous blood flow of 150 ml/min [2, 3] (row 5). Row 6 shows the per cent of the agent lost from blood through the skin. In row 7 the percutaneous loss/min/1.8 m² (average adult surface area) is calculated. The loss of nitrous oxide would be about 380 ml/hr in an average-sized adult (6.4 ml/min/m² × 60 minutes). The per cent of total body uptake that percutaneous loss represents is shown in row 9. Converted to percutaneous loss at identical alveolar concentrations, nitrous oxide and ether have similar loss rates while cyclopropane and halothane are comparable (row 10). Row 11 compares the percutaneous losses of cyclopropane, ether and halothane with that of nitrous oxide at 1 per cent alveolar concentration.

Figure 1 shows percutaneous losses in ml /m²/min/1 per cent alveolar concentration plotted against duration of anesthesia.

Figure 2 shows the effects of changing skin temperature on the percutaneous loss of nitrous oxide at an alveolar concentration of 70 per cent. Loss is related to skin temperature in nearly a rectilinear manner over the temperature range studied.

Discussion

In contrast to the decrease with time of total body uptake of an inhalational anesthetic, the percutaneous loss increases, reaching a plateau between 60 and 100 minutes. The percutaneous loss of nitrous oxide represents about 6.4 per cent of the total body uptake of 100 ml /min [4] after the first 100 minutes (table 2, row 8). Other workers have reported values of less than 100 ml/min [5, 6] after the first 60 minutes of anesthesia. If this is the case, skin loss after 100 minutes represents an even larger share of the total uptake. We calculate that the percutaneous loss of cyclopropane represents 2.5 per cent of total uptake after 100 minutes.[7] Again, as total uptake decreases with time, the percutaneous loss will represent a larger proportion, but not to the same degree as seen with nitrous oxide. Percutaneous losses of ether and halothane represent even smaller proportions of total uptake [5, 9] (table 1, row 9) and it is unlikely that loss through the skin ever represents a significant portion of the uptake except after very long periods of administration for either of these agents.

Percutaneous loss at a given partial pressure (table 2, rows 10 and 11) is related inversely to the fat/blood partition coefficient (table 2, row 4). Halothane, with the greatest fat solubility (also the greatest molecular weight) had the smallest percutaneous loss. Cyclopropane, with a blood solubility almost equivalent to that of nitrous oxide (and identical molecu-

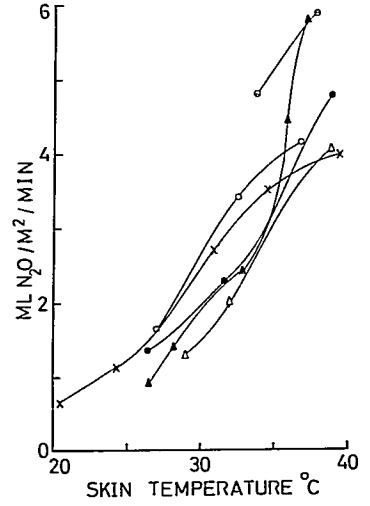

FIG. 2. Percutaneous loss of nitrous oxide/m²/min at an inspired concentration of 70 per cent plotted against skin temperature. Each curve represents a separate experiment and each point an individual determination (corrected to 0 C). Loss increases in a rectilinear manner as skin temperature increases from 20 to 40 C.

lar weight) but seven times more fat-soluble, showed a smaller percutaneous loss than nitrous oxide. Ether had the greatest blood solubility, but its fat/blood partition coefficient was near that of nitrous oxide and percutaneous loss when corrected to loss per 1 per cent alveolar concentration was similar. The inverse relationship of fat solubility and percutaneous loss may be due to the subcutaneous fat layer. This layer may act as a pool or sink into which anesthetic may move from the dermal layer. The sink would be largest for the anesthetic with the highest fat/blood partition coefficient. This reduction in the dermal anesthetic partial pressure by intertissue diffusion has been suggested by Perl.[11]

The finding that only 7.2 per cent of the nitrous oxide is lost from the blood flowing through the skin suggests that nitrous oxide transfer across the skin is limited more by diffusion than by flow. Even smaller percentages of the other anesthetics are lost (table 2, row 6), suggesting that diffusion poses an even greater barrier to these gases. These calculations assume a cutaneous blood flow of only 150 ml/min/m². We (unpublished data) have found that cutaneous perfusion is considerably elevated above awake values during halothane and cyclopropane anesthesia. Therefore, the loss through the skin is probably an even smaller fraction than we have indicated.

Neither tissue solubility (which decreases with increasing temperature) nor the diffusion coefficient, which increases only about 1 per cent per degree C temperature increase,[12] can explain the large variation in percutaneous loss with variations in skin temperature (fig. 2). The large increase with increasing temperature may be explained by the opening of additional capillaries nearer the skin surface (and away from subcutaneous fat), which decreases the path length for diffusion. Likewise, opening additional capillaries in areas of low capillary density would increase the surface area for diffusion. These same conclusions have been suggested by Klocke *et al.*,[13] from their studies of the losses of argon, helium and nitrogen through the skin at various ambient temperatures.

The transference of our data, obtained from a limited portion of skin, to the entire body surface must be viewed with some reservations. The effective body surface area is seldom equal to the total body surface area. In our studies that portion of the forearm and hand in direct contact with the glass chamber may not have participated in percutaneous loss to the same extent as the remaining skin surface. Similarly, drapes covering the skin or pads supporting the body may not allow effective gradients to exist. If diffusion is the limiting factor in percutaneous loss, then variation in skin thickness will also alter loss rates.

Halothane (Fluothane®) for these studies was donated by Ayerst Laboratories.

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Drugs

NARCOTIC ANTAGONIST A study was performed in volunteers to determine the relative degrees of respiratory depression produced by nalorphine and morphine and their interaction when administered together. The relative potency of nalorphine when compared with morphine was found to be 0.74; that is, 13.5 mg nalorphine produced depression in respiration approximately equivalent to 10 mg morphine. The data also suggest that antagonism of the respiratory effects of morphine by nalorphine is related primarily to differences in intrinsic activity of the drugs and not solely to receptor affinity. Their interaction could thus be classified as competitive dualism. (*Bellville, J., and Fleischli, G.: The Interaction of Morphine and Nalorphine on Respiration, Clin. Pharmacol. Therap. 9: 152 (March) 1968.*)

RESERPINE Hypertensive patients were studied before and after 30 days of treatment with reserpine. Cardiac output, measured both at rest and after induced atrial tachycardia, was found to be reduced approximately 25 per cent after reserpine treatment, while resting pulse was little affected. Atrioventricular conduction time increased significantly after reserpine. These results indicate that reserpine may lower cardiac output at rest significantly with no further decrease during atrial tachycardia. Reserpine may enhance second-degree heart block during induced atrial tachycardia. (*Cohen, S. I., and others: Effects of Reserpine Therapy on Cardiac Output and Atrioventricular Conduction During Rest and Controlled Heart Rates in Patients with Essential Hypertension, Circulation 37: 738 (May) 1968.*)