Uptake of Halothane by the Human Body

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THE rate of uptake and equilibration of the body with cyclopropane was previously analyzed in this laboratory.[1] The experiments now to be presented were carried out using halothane, an inhalational anesthetic with considerably different physico-chemical properties.[2] Its uptake and subsequent output were obtained by continuous measurement of expired gas concentration in normal subjects who breathed a fixed gas mixture at a constant rate for approximately two hours. When compared with cyclopropane, saturation of the tissues of the body with halothane proceeds slowly. This difference probably reflects the relatively great solubility of halothane in blood and other tissues.

Methods

The subjects were volunteers who received no drugs other than halothane. They were studied in the supine position while breathing through a mouthpiece and unidirectional valve (fig. 1). The nostrils were occluded. Respiratory rate and depth were controlled with a chest cuirass respirator. Tidal volume was adjusted to twice normal and respiratory rate to 9–11 /minute. Following a period of air breathing with the cuirass respirator in operation, a halothane-air mixture was connected to the airway for the uptake study. After 1.5 to 2 hours, halothane was discontinued and the subject breathed room air for an additional 0.5 to 1 hour while the measurements were continued.

In order to minimize pharmacologic effects on circulation or respiration, the inspired concentration of halothane was intentionally limited to the lowest level which could be accurately measured (0.2 per cent). The gas mixture was prepared in a large high pressure cylinder and delivered to a 5-liter reservoir bag via a regulator and flowmeter and thence through a nonrebreathing valve to the subject. Since the flow of gas never completely distended the bag, the nonrebreathing valve remained competent. The inspiratory valve did not open until the beginning of inspiration and stayed closed during expiration. Air could not be aspirated through the expiratory valve.

A portion of the respired gas was drawn continuously at a rate of 600 ml./minute from the lumen of the mouthpiece through a needle and a lead tube to a halothane and then to a CO_2 infrared analyzer. The volume withdrawn was accounted for in the calculations. The analyzers were standardized using known gas mixtures. Experiments with square wave concentrations of halothane in air showed that there was at least a 95 per cent response of the analyzer within two seconds, during which a tenfold washout of the analyzer occurred. The duration of expiration in this study averaged four seconds. It was estimated from nitrogen washout studies that alveolar air was sampled within one second, consequently three seconds were available to measure the end-expired concentrations.

The temperature of the respired gases was measured continuously with a copper-constantan thermocouple inserted through a needle into the lumen of the mouthpiece. The respiratory minute volume was measured by passing the exhaled gases through a dry gas volume meter. With each revolution the meter's pointer touched the cone of a radio loudspeaker which produced an electrical signal. It was estimated from preliminary studies that measurement of minute ventilation was accurate to $\pm$ 0.5 liter/minute. The minute ventilation varied by no more than $\pm$ 0.5 liter/minute. Gas volumes were corrected to BTPS. Lead 2 of the electrocardiogram was obtained. All measurements were recorded on a 6-channel polygraph.

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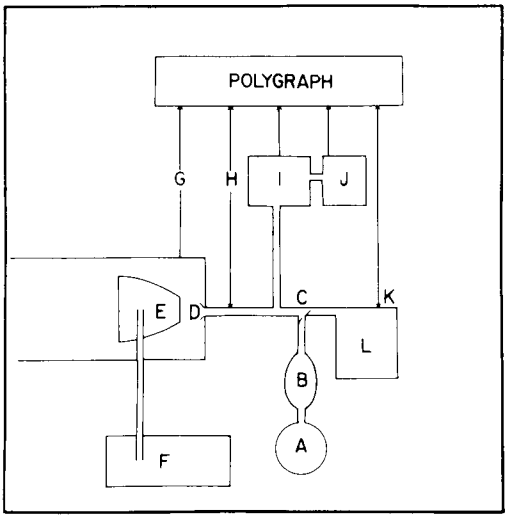

FIG. 1. Apparatus. *A*, high pressure cylinder containing 0.2% halothane in air; *B*, 5 l. reservoir bag; *C*, unidirectional valve; *D*, mouthpiece; *E*, *F*, chest cuirass respirator; *G*, ECG; *H*, thermocouple; *I*, halothane infrared analyzer; *J*, CO_2 infrared analyzer; *K*, loudspeaker; *L*, dry gas volume meter.

The diluting effect of water vapor on the expired halothane concentration was corrected for by subtracting the water vapor pressure from the total ambient pressure. Exhaled air at the mouth was taken as 80 per cent saturated with water vapor at the end of expiration [3] while gas drawn from the supply cylinder was dry. The correction factor is:

$$\frac{P_B - S_I \quad (P_{H_2O})}{P_B \quad S_E \quad (P_{H_2O})}$$

where P_B = barometric pressure, S = fractional saturation with water vapor, and P_{H_2O} = water vapor pressure at the temperature measured. The correction factor during the uptake period calculated in each case averaged 1.05. During the output period the correction was lower (1.02) because the inspired air was maintained at 50 per cent saturation by the air conditioning system.

Since there was essentially no infrared absorption by water vapor at the wave lengths used for halothane analysis, there was no base line shift due to the presence of water vapor in the expired air. The halothane concentration in the respired gas was overestimated (average 2 per cent) because of the collision broadening effect of the water vapor present. The error probably affected the inspired and expired values since gas in the mouthpiece was wet both at the end of inspiration and of expiration.

Carbon dioxide interfered with the halothane analysis because its infrared absorption spectrum overlapped that of halothane. This interference was eliminated by filling the analyzer case with carbon dioxide. No collision broadening effect was noted with carbon dioxide concentrations up to 8 per cent.

No correction was made for the concentrating effect of halothane absorption, since calculations showed that the maximum correction would be less than 0.75 per cent and that it would decrease as the study progressed. Nor was a correction made for difference between the volume of carbon dioxide expired and the volume of oxygen absorbed.

Results

A measure of the degree of equilibration between the tissues and an inspired gas is the relation of the end-expired and inspired gas concentrations. This relation expressed as the ratio F_A/F_I is zero when inhalation of the gas starts and attains unity when uptake by the body ceases and equilibrium is achieved. Table 1 present F_A/F_I ratios determined at various times following the beginning of halothane inhalation. The data for a typical case are shown in figure 2.

The halothane concentration ratio F_A/F_I did not mount rapidly. At one minute, the average end-expired gas concentration in the eight

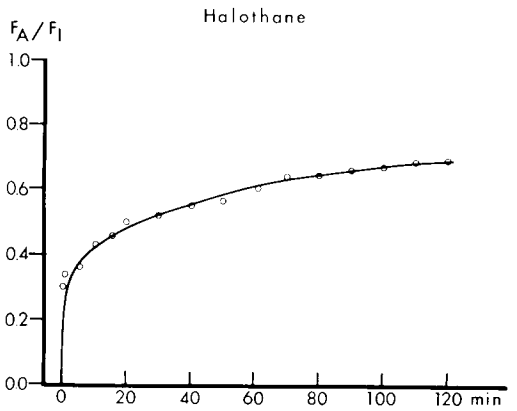

FIG. 2. Ratio of end-expired and inspired halothane concentrations (F_A/F_I). (Subject 61-14).

TABLE 1. Ratio of End-expired and Inspired Halothane Concentrations (F_A/F_I)

Subject: Uptake Minutes	61-09 F_A/F_I	61-10 F_A/F_I	61-11 F_A/F_I	61-12 F_A/F_I	61-13 F_A/F_I	61-14 F_A/F_I	61-15 F_A/F_I	61-16 F_A/F_I
Sex	M	M	F	M	F	M	M	F
Age, years	19	20	20	21	20	28	26	23
Ht., cm.	180	187	164	173	162	180	178	163
Wt., kg.	62	88	55	77	52	71	77	76
S.A., m².	1.77	2.14	1.58	1.90	1.52	1.88	1.93	1.80
$\dot{V}_T$, l./min.	9.2	8.7	5.6	10.4	9.1	6.6	7.8	9.0
P_{ECO_2} (start-end)	36–29	26–32	31–43	38–26	32–30	27–30	44–42	32–31
1	0.30	0.38	0.29	0.36	0.41	0.34	0.32	0.52
5	0.48	0.50	0.38	0.49	0.52	0.37	0.37	0.64
10	0.52	0.59	0.48	0.55	0.59	0.43	0.43	0.66
20	0.59	0.63	0.62	0.62	0.68	0.50	0.50	0.71
40	0.62	0.64	0.66	0.72	0.72	0.56	0.56	0.71
60	0.64	0.65	0.71	0.72	0.73	0.61	0.65	0.73
90	0.70	0.68	0.73	0.80	0.77	0.66	0.65	0.74
120	0.75	0.75		0.79	0.82	0.69		
Output Minutes								
1	0.36	0.31	0.42	0.40	0.33	0.38	0.34	0.30
5	0.19	0.25	0.28	0.31	0.24	0.22	0.24	0.21
10	0.19	0.21	0.22	0.21	0.18	0.21	0.20	0.15
20	0.14	0.16	0.17	0.18	0.15	0.18	0.17	0.13
30	0.11	0.11	0.12	0.17	0.14	0.17	0.13	0.08
40				0.16	0.12	0.15	0.11	0.06
60				0.11				

subjects was 0.36 (range 0.29–0.52) of that inspired; 0.47 (0.36–0.64) at five minutes; and 0.53 (0.43–0.66) at ten minutes. At 40 minutes a concentration ratio of 0.65 (0.55–0.72) was reached, after which it rose more slowly to attain 0.76 (0.69–0.82) at two hours. Subjects with greater ventilation showed a more rapid rise in the F_A/F_I ratio (see subjects 61-12 and 61-14).

One minute after inhalation had ceased, the average end-expired gas concentration had decreased to 0.36 (range 0.30–0.42) of the halothane concentration inspired during the uptake period. By ten minutes its was 0.20 (0.15–0.22), and still 0.12 (0.06–0.16) at 40 minutes.

Discussion

These findings are in marked contrast to those obtained with cyclopropane.[1] Within ten minutes of the start of inhalation the end-expired cyclopropane tension attained 90 per cent of that inspired, whereas for halothane the comparable figure was only 50 per cent. Within 30 minutes the F_A/F_I ratio averaged 0.95 for cyclopropane, but only 0.64 for halothane. The greatest ratio observed in any halothane uptake study was 0.82 at two hours

Since physiological variables such as body size and ventilation rate were closely comparable in the present and previous studies, it is likely that differences in results are to be attributed to contrasting physical properties of cyclopropane and halothane. Despite its large molecular weight (197) there appears no reason to suspect that halothane uptake is diffusion limited. On the other hand a relatively slow equilibration rate between inspired air and arterial blood would be predicted for halothane on the basis that its blood/gas partition coefficient is five times that of cyclopropane.[2, 4] In addition, tissue/blood partition ratios for halothane in a number of human tissues exceed unity, while those for cyclopropane are substantially lower.[2, 5]

The measured rates of equilibration were

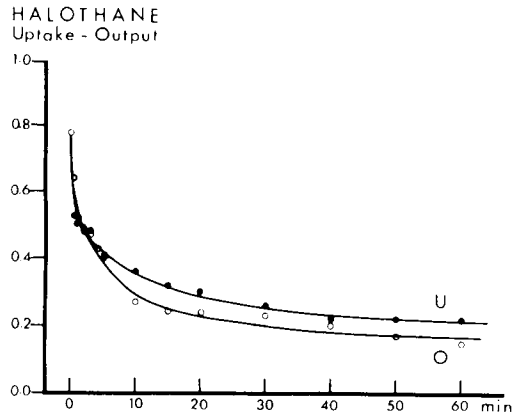

FIG. 3. Saturation and desaturation curves compared. (Subject 61-12). *O*, ratio of end-expired halothane concentration during desaturation period and halothane concentration inspired during the saturation period; *U*, the complement of the ratio of end-expired and inspired halothane concentrations during the saturation period $(1 - F_A/F_I)$.

compared with rates predicted from Kety's equation no. 55 [6] by substituting measured and assumed normal physiologic [7, 8] values, blood/gas partition coefficient of 2.3 [2] and tissue/blood partition coefficient of 3.[2] As was previously found for cyclopropane,[1] the measured values initially increased at a faster rate than the predicted values. The difference increased until 40–60 minutes, when the measured ratio was 25–50 per cent higher than that predicted. After that the measured values increased at a progressively slower rate and fell below those predicted at two hours. The cause for this discrepancy is thought to be the same as that observed with cyclopropane, namely that Kety considered the body to be a homogeneous mass in which inhaled gas is uniformly distributed.

Analysis of the data can yield information concerning the types of tissues undergoing saturation, and the limitations imposed by the solubility of halothane. At periods greater than 1.5 hours end-expired concentrations of halothane had achieved relatively steady values. An estimate of arteriovenous concentration differences of halothane at this time was obtained by dividing calculated halothane uptake rate by an assumed normal value [7] for cardiac output. Rate of uptake was calculated by multiplying estimated alveolar ventilation [9] and the difference between end-inspired and end-expired halothane concentrations. The calculated arteriovenous differences averaged 13 per cent (range 9–18 per cent) of the arterial tension, suggesting a substantial lack of equilibration between slowly perfused watery tissues (*e.g.*, muscle) and blood at this time.

The reasoning behind this interpretation is as follows: The viscera, constituting about 6 per cent of body mass, receive 70 per cent of the cardiac output. Presumably these organs will rapidly approach equilibrium with blood. When they reach equilibrium the arteriovenous difference must be less than 30 per cent of the arterial tension. Among the remaining tissues, fat is most poorly perfused in relation to its ability to acquire halothane; for this reason fat should approach equilibrium more slowly than any other tissue. If all the tissues of the body except depot fat (receiving 5–7 per cent of the cardiac output) had attained equilibrium, the arteriovenous halothane difference would necessarily be less than 5–7 per cent of the arterial content. The intermediate concentration differences observed in this study therefore suggest that slowly perfused watery tissues are still taking up halothane.

Additional evidence to identify tissues important in halothane uptake was obtained by graphic curve fitting. The rates of change of $(1 - F_A/F_I)$ determined in four subjects studied were plotted semi-logarithmically against time. The resulting curves represented the sum of a series of lines of successively decreasing slopes. Uptake rate could be expressed as a sum of exponential functions each possibly reflecting events at a specific tissue. The time constant of the slowest component of the uptake curves ranged from 300 to 500. By way of comparison, a constant of 3 can be estimated for viscera, 100 for muscle and 2000 for fat. Since the greatest time constant observed is only a fraction of that calculated for fatty tissue, it follows that other tissues must still be engaged in the uptake of halothane.

The saturation and desaturation curves were not symmetrical, F_A falling more rapidly during desaturation than it rose during saturation (fig. 3). This discrepancy probably was caused by failure to achieve equilibration be-

tween the slowly perfused tissues and the inspired gas during the uptake period. Despite the rapid initial decline of F_A, the rate of change became progressively smaller, and at 40 minutes F_A still averaged about 20 per cent of the highest value observed during saturation.

These data lead to a number of clinical implications. It is unlikely that the administration of a safe halothane concentration will cause the alveolar tension of halothane to approach an anesthetic level quickly. For rapid induction of halothane anesthesia, high concentrations of the agent must be administered, and ventilation must be maintained. The inspired concentration must be reduced propressively as the alveolar concentration rises. Similar control of the alveolar concentration is not possible during desaturation (recovery). Consequently, slow elimination from the body is a cause of delayed awakening following halothane administration.

Mapleson [10] has calculated the ml./minute uptake of halothane in fully anesthetized patients undergoing surgery. There was considerable scatter from subject to subject and "rapid fluctuation in ventilation" and uptake. The major difference between his study and this is that we administered a subanesthetic gas concentration to young, normal volunteers. Thus, changes in circulation and respiration were presumably avoided, and we also precluded the possibility that the uptake process might be affected by drugs other than halothane or by surgical stimulation.

In order to compare Mapleson's data with ours, his mean uptake values (ml./minute/percentage inspired concentration) were converted to F_A/F_I values. The mean equilibration rate in the present study increased more rapidly than in Mapleson's study. The difference is probably related to the difference in ventilation.

Summary

The uptake and subsequent output of halothane by the body were studied by continuous measurement of expired gas concentration in eight normal subjects who breathed a fixed (0.2 per cent) gas mixture at a constant rate for 1.5–2 hours. The ratio of end-expired to inspired gas concentrations did not mount rapidly, the average reaching only 0.53 within ten minutes. The greatest ratio observed in any uptake study was 0.82 at two hours. The expired concentration fell more rapidly during the output period than it rose during uptake. Compared to most other inhalational anesthetics, both uptake and output of halothane proceed slowly. This difference is probably attributable to the relatively great solubility of halothane in blood and body tissue.

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