Halothane Uptake in Man at Constant Alveolar Concentration

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Sechzer et al. and Mapleson determined halothane uptake in man at a constant inspired tension. Their technique consisted of measuring inspired and alveolar concentrations of halothane. Knowing this and alveolar tidal volume it was possible to calculate uptake. We have repeated this study but have made alveolar rather than inspired concentration constant.

Method

Ten healthy patients (average age 40) who were to undergo various operative procedures were premedicated with atropine 1.2-1.6 mg. Anesthesia was induced with 200 to 550 mg. (average 400 mg.) of thio[pentan]. Following relaxation with succinylcholine, the trachea was sprayed with cocaine (100-150 mg.) and intubated. Immobility was maintained during the experimental observations with a continuous succinylcholine drip. The endotracheal tube was connected to a nonbreathing system as diagrammed in figure 1. Inspired and end-tidal halothane concentrations were measured with an infrared analyzer. The analyzer head was filled with 100 per cent carbon dioxide plus a few drops of water to eliminate the cross-over effects of these gases on halothane. Both expired and inspired samples registered zero on the halothane meter when pure oxygen was respired. Calibration of the analyzer has been previously discussed. End-tidal gas was obtained by drawing samples at end-expiration from the patient end of a 30-ml. dead space interposed between endotracheal tube and nonrebreathing valve. The reservoir served to prevent contamination of end-tidal gas.

Halothane-oxygen administration was begun 5 to 15 minutes after the last dose of thio[pentan]. Readings were taken every minute for the first ten minutes and every ten minutes thereafter until the end of the surgical procedure. Operation began on an average of 20 minutes after halothane administration was begun. End-tidal halothane concentration was held constant by adjustment of inspired concentration. At this concentration systolic blood pressure usually remained within 20 mm. of mercury of the patient's normal pressure.

Respiration was maintained through a Ventimeter with a constant pressure ventilator. Tidal volume was determined at intervals by observation of volume change during inspiration while inflow was shut off. From this was subtracted volume change with inflow off and endotracheal tube clamped. This corrected for compliance of the system. Average tidal volume was 600 ml. and mean rate per minute was 14. This resulted in an average end-tidal $P_{CO_2}$ of 20 mm. of mercury as measured on random samples by the carbon dioxide electrode. Alveolar tidal volume was estimated as tidal volume times 0.745. The figure 0.745 was determined by analysis of end-tidal and mixed expired carbon dioxide concentrations from eight patients treated in a manner identical to that in this study. The average mixed end-tidal divided by alveolar carbon dioxide concentrations gave the 0.745 figure when the tidal volume varied from 500-700 ml. Increasing the tidal volume resulted in no significant change. The average figure was 0.758 for tidal volumes varying from 800 to 1,500 ml. On the other hand below 400 ml. the figure became considerably smaller. This agrees with Nunn and Hill's work on the relation of alveolar tidal volume to tidal volume except that our figure is slightly higher (Nunn and Hill report a figure of 0.68). The discrepancy is not real, however, since we used alveolar rather than the correct arterial carbon dioxide tension. If the alveolar-arterial

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carbon-dioxide gradient under anesthesia is taken as 4 mm. of mercury our figure reduces to 0.645, which is close to 0.68. Whether a similar gradient exists for halothane is not known. In the theoretical descriptions we have assumed it does not exist. The error such an assumption might introduce is small, amounting to less than a 10–15 per cent shift of uptake. Alveolar minute volume was then obtained by multiplying alveolar tidal volume by rate. Intermittently during the procedure the lungs were expanded to double or triple the normal volume to reduce any tendency to develop atelectasis.

Uptake of halothane vapor per minute was determined as (inspired concentration minus end-tidal concentration) × (alveolar minute volume). Uptake obtained was corrected to uptake per 70 kg. by multiplying times 70 kg./patient’s weight. A final correction to uptake at an alveolar concentration of 0.8 per cent was made by multiplying by 0.8/actual alveolar concentration. We selected 0.8 per cent because it was found to be the minimal alveolar concentration required for anesthesia. No correction was made for water vapor or volume change due to agent uptake, both of these being minor factors involving a relative change of less than 5 per cent.

Comparison of experimental data was made against data from a mathematical model described previously. Briefly the model assumes a constant arterial (alveolar) tension. Flow to tissues is divided between four groups with properties as outlined in table 1. Uptake by any one tissue group is obtained by use of the equation: $V_{AT} = K_t (1 - e^{-K_s T})$, where $V_{AT}$ is the volume of halothane in the tissues at time $T$, $K_t$ is a constant equaling the tissue/blood partition coefficient times volume of the tissue, times the blood concentration of halothane. Blood concentration is determined from the known blood/gas partition coefficient of 2.3 times 0.008. $K_s$ is a constant equaling blood flow per unit volume of tissue divided by the tissue/blood partition coefficient. Total uptake is obtained by summation of uptake in the four tissue groups.

Finally, we predicted the halothane concentration in the circle system and of the gas flowing into the circle (inflowing concentration) required to maintain a constant alveolar concentration of 0.8 per cent during clinical anesthesia using a rebreathing system. These calculations assume complete and immediate mixing of all gases entering the circle. The

<table>
<thead>
<tr>
<th>Tissue Group</th>
<th>Total Volume (liters)</th>
<th>Perfusion (liters/minute)</th>
<th>Tissue/Blood Partition Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRG</td>
<td>6.0</td>
<td>4.5</td>
<td>2.5</td>
</tr>
<tr>
<td>MG</td>
<td>33.0</td>
<td>1.1</td>
<td>3.5</td>
</tr>
<tr>
<td>FG</td>
<td>14.5</td>
<td>0.32</td>
<td>60.0</td>
</tr>
<tr>
<td>VPG</td>
<td>12.5</td>
<td>0.09</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Results and Discussion

Figure 2 graphically shows the results on mean uptake of halothane vapor per 70 kg at 0.8 per cent alveolar concentration. Uptake falls rapidly at first from a high of 81 ml uptake during the first minute to 47 ml uptake per minute at five minutes and to 34 ml at 10 minutes. At 20 minutes uptake is 28 ml and thereafter falls slowly until at 160 minutes it equals 12 ml. In two operations which lasted over four hours uptake reached 10.8 ml and 5.6 ml per minute. Considerable variation in uptake occurred, the mean standard deviation equals one-third of the uptake figure.

Although the experimental and theoretical curves closely parallel each other (fig. 2), minor discrepancies may be seen, especially during the first 10–20 minutes of uptake. These, in part, are related to the variation normally found in any in vivo study. They may also be related to the conditions of the study. For example, hyperventilation would reduce cerebral blood flow and hence uptake during the first five to ten minutes. This coincides with the experimental finding that actual uptake was initially slightly lower than predicted. If cerebral blood flow were reduced, it would also mean that uptake by brain although reduced would continue for a longer period of time. This coincides with the experimental finding that uptake is greater than predicted at 10 and 20 minutes. Unfortunately, without actual data, the above concepts are no more than speculation.

If alveolar anesthetic concentration equals brain concentration then a constant alveolar concentration reflects a relatively constant “depth” of anesthesia. The above figures thus provide a guide to the average amount of halothane required to maintain a stable light level of anesthesia in a closed system. Deeper anesthesia would require somewhat greater quantities. Increase in alveolar concentration would not result in a proportional increase in uptake because of the probable concomitant decrease in cardiac output.

As may be seen in figure 2, predicted and actual uptake of halothane coincide closely. This is in contradistinction to the divergence noted when the same equations were used to predict uptake at a constant inspired tension. These equations are capable of predicting anesthetic uptake of inert anesthetics (at a constant alveolar concentration) ranging from relatively insoluble agents (nitrous oxide and cyclopropane) to moderately soluble (halothane) and very soluble agents (ether).

Figure 3 compares the results obtained with those of Sechzer, Linde and Dripps. The difference between the two is apparent: change in uptake with time at a constant alveolar concentration is relatively much greater than when inspired concentration is held constant. The difference between the two techniques is related to solubility. Agents of low solubility such as nitrous oxide or cyclopropane demon-
is necessary at first. This falls to a "knee" at about ten minutes. Thereafter the required concentration continues to fall at a much slower rate. With hyperventilation (8 liters/minute) the inspired concentration is not far from alveolar but with hypoventilation (2 liters/minute) even after 100 minutes of anesthesia, inspired concentration must be double that in the alveoli in order to maintain the latter constant.

Figure 5 shows the calculated inflowing concentration required in a circle anesthetic system to maintain alveolar concentration at 0.8 per cent. Alveolar ventilation is constant at 4 liters/minute. The higher the inflow rate the lower need be the inflowing concentration. Conversely using low "economy" flows of 1 to 2 liters/minute on induction requires an initial concentration of 10 per cent and even after 100

![Graph showing uptake of halothane over minutes](image_url)

**Fig. 3.** The data of Sechzer, Linde and Dripps (closed circles and broken line, left ordinate scale) are here compared with the results of this study (open circles and continuous line, right ordinate scale). Sechzer's data is obtained with patients breathing 0.2 per cent halothane. Uptake is calculated from \(0.002(1 - F_E/F_I)\) times alveolar ventilation (personal communication from P. H. Sechzer). \(F_E\) is the fractional halothane concentration in end-expired air, and \(F_I\) is the fractional inspired halothane concentration.

strate only a slight difference, but the difference with one of high solubility such as ether may be enormous. A moderately soluble agent such as halothane shows an appreciable but moderate difference.

Using either the experimental or theoretical values for uptake, it is possible to predict the concentration of agent which must exist in an anesthetic circle and in total inflow to the circle in order to maintain a constant alveolar concentration. The inspired concentration required is shown in figure 4. Alveolar halothane is held at 0.8 per cent. The three curves show the calculated inspired concentration required to maintain the 0.8 per cent alveolar concentration when alveolar ventilation is 2, 4, or 8 liters/minute. All curves in both figures 4 and 5 follow the same pattern. A high but rapidly decreasing concentration

![Graph showing alveolar concentration vs. minutes](image_url)

**Fig. 4.** The calculated inspired concentrations of halothane required to maintain a constant alveolar concentration of 0.8 per cent when ventilation is altered as indicated. Uptake is that found in figure 2.
minutes the inflow concentration must be two and one-half to three times that in the alveoli. At higher flows of 4 to 8 liters/minute induction concentrations of 4 to 5 per cent halothane are reasonable but must be rapidly reduced within ten minutes to 2 per cent.

The construction of most circle systems produces a system which does not exactly follow the calculated curves. Inflow location on the inspiratory side of the circle combined with the overflow valve location at the Y-piece or on the expiratory side of the circle results in a more efficient system. Efficiency of such an arrangement may approach that of a non-rebreathing system. Optimally, inflow concentration might even approach (but never be lower than) the required inspired tension. This results (1) from the incomplete dilution of inflow gas with system gas before inspiration and (2) from the overflow loss of gas containing mainly alveolar air. The end result is that the clinically required inflow concentration lies between the predicted inflow and inspired (circle) concentrations.

Clinically, if ventilation is increased perhaps by changing from spontaneous to controlled ventilation, the concentration in the circle must be decreased if the anesthetic level is to remain constant. Conversely a decrease in ventilation requires an increase in circle concentration. During induction where uptake is high and variable, a high inflow (10+ liters/minute) is the best method of controlling circle concentration (unless a halothane analyzer is available). As uptake diminishes, inflow may be gradually reduced to 2 to 4 liters/minute.

Although a certain halothane concentration may be delivered into an anesthetic system there is no rigid correlation between the percentage halothane and that found in the alveoli. One cannot merely by knowing the inflowing concentration know the effective anesthetic concentration. The latter as we have shown will also be determined by inflow rate, ventilation, and by uptake.

Summary

Uptake of halothane at a constant alveolar concentration was determined in ten healthy human beings. Uptake was high at first and rapidly decreased during the first 20 minutes.

At 0.8 per cent alveolar concentration uptake was 81 ml. per minute at one minute, 47 ml. at five minutes, 34 ml. at ten minutes, and 28 ml. at 20 minutes. Uptake decreased slowly thereafter until at 160 minutes it was 12 ml. per minute. This rate of uptake paralleled that predicted mathematically using a four-compartment model of the body.

The appreciable and constantly diminishing uptake was shown to have the following implications: anesthetic level may not be related rigidly to inflowing concentration in an anesthetic system; instead anesthetic level must be appreciated as being the result of numerous factors including inflow rate and concentration, ventilation, and uptake.

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References


SERUM HEPATITIS  The virus of hepatitis survives indefinitely below 10° C. The higher the storage temperature, the more readily does the virus become inactivated. The limiting factor is that heat may denature the plasma proteins. Coincidental serum hepatitis from another source, or infectious hepatitis, may occur. Infectious hepatitis was reported 100,000 times in the United States in 1961, and may be expected as a coincidence during the 180 day post-transfusion period in one patient out of each 5,000 transfused. (Allen, J. G.: Susceptibility to Serum Hepatitis, Arch. Surg. 85: 875 (Dec.) 1962.)

ACUTE PANCREATITIS  To be effective, bilateral splanchnic block must be obtained, but this may result from a single injection on one side only. Pain is relieved only when bilateral spread of the agent occurs. Relief may be striking and may be permanent. If relief is temporary, the procedure can be repeated and an indwelling fine catheter may be used to facilitate repeated injections. (DeJode, L. R., and Howard, J. M.: Management of Patients with Acute Pancreatitis, Surg. Clin. N. Amer. 42: 1489 (Dec.) 1962.)

SUBARACHNOID DRUG DISTRIBUTION  Distribution of antibiotics following injection into the lumbar sac was demonstrated by autoradiography and constant radiography in monkeys and by three-dimensional external scanning, autoradiography and histologic observation in human patients. The volume of injected solution was determined to be the primary factor in obtaining widespread distribution. A volume equivalent to 10 per cent of the estimated cerebrospinal fluid volume produced the distribution of the drug in significant concentration to the level of the basal cisterns. When a volume equivalent to 25 per cent of the estimated cerebrospinal fluid was injected in monkeys, distribution was obtained throughout the cerebral subarachnoid space and ventricular systems. (Rieselbach, R. E., and others: Subarachnoid Distribution of Drugs after Lumbar Injection, New Engl. J. Med. 267: 1273 (Dec. 20) 1962.)