THE RATE OF UPTAKE OF HALOTHANE VAPOUR IN MAN

BY

W. W. MAPLESON

Department of Anaesthetics, Welsh National School of Medicine, Cardiff, Wales

One of the factors affecting the concentration of anaesthetic inspired by a patient from a closed anaesthetic circuit is the rate of uptake of the anaesthetic by the patient (Mapleson, 1960; Galloon, 1960; Mushin and Galloon, 1960). This investigation was undertaken to determine the rate of uptake of halothane.

METHOD

Principle. The basis of the method was to administer to patients a constant concentration of halothane in oxygen, to measure the difference between the inspired and mixed-expired concentrations (by means of a thermal-conductivity meter or katharometer) and to multiply this difference by the measured total ventilation.

Measurement procedure. The circuit is shown in figure 1. The constant inspired concentration was obtained by passing oxygen through a Fluotec vaporizer. The output passed through a mixer into the inspiratory reservoir bag (I). The mixer ensured that the sample drawn for analysis was truly representative of the inspiratory mixture. The patient inspired from the reservoir bag via the one-way valve (A), the Dräger volumeter and the corrugated breathing tube. The patient's expirations passed along another length of corrugated tube, through a Waters canister and a one-way valve (C) into the expiratory reservoir bag (E) and finally to the atmosphere via valve D.

The oxygen flow through the Fluotec was normally fixed at 6 l./min. The patient's total ventilation was usually less than this and the excess gas escaped through valve B, which was arranged to open at a lower pressure difference than valve A. On a few occasions hyperventilation made it necessary to increase the oxygen flow for a few minutes to prevent the inspiratory bag from emptying.

A sample of the inspiratory mixture was drawn at a rate of about 800 ml/min from a point between the mixer and the inspiratory reservoir bag, passed through one side of the katharometer and then returned to the anaesthetic circuit slightly downstream of the sampling point. A sample of mixed-expired gas was drawn at the same rate from the expiratory reservoir bag and passed through the other side of the katharometer and then out to the atmosphere.

The katharometer responds to the difference of thermal conductivity between the two gas streams flowing through it. For this difference to be a measure of the difference in halothane content the other constituents of the gas mixture must be the same in both streams. Accordingly a Waters canister filled with soda lime was used to absorb carbon dioxide from the patient's expirations.

Similarly it would have been logical to use a drying agent to remove water vapour from the expiratory sample, but when silica gel was used it was found to absorb halothane as well as water vapour. In retrospect it appears that it would have been possible to use a different type of drying agent which did not absorb halothane; but in fact the alternative approach was adopted of rendering the humidity of both gas streams the same. In another connection it had been noticed that soda lime had the property of regulating the humidity of a gas stream within quite close limits, and this property was exploited here. Both sample streams were passed through small soda-lime canisters (X, Y) but, since the expiratory sample was first saturated by its passage through the soda lime in the Waters canister, the inspiratory sample was moistened by first passing it through the rough humidifier shown in figure 1. Measurements were made of the humidity of the two gas streams entering the katharometer under the various experimental conditions and any differences observed were inter-
The circuit. The parts concerned with the administration of the halothane to the patient are shown as wide tubing; the parts concerned with the analysis of the difference between the inspired and mixed-expired concentrations are shown as narrow tubing.

Interpretation in terms of the errors they would introduce in the calculated rates of uptake of halothane vapour. It was found on calculation that any systematic error would be unlikely to exceed 1 per cent of the true rate of uptake and any random error would be unlikely to exceed 1 ml of halothane vapour per minute.

The absolute value of the inspired concentration was determined from a calibration of the Fluotec; at some time during each day of experimenting, the output of the Fluotec, for the oxygen flows and tap settings used during the day, was determined by passing the output through one side of the katharometer and oxygen through the other.

The zero of the katharometer was checked by passing oxygen through both the reference and the sample channels. The sensitivity was determined by keeping oxygen as the reference gas and passing through the sample channel a mixture of halothane and oxygen produced by bubbling oxygen via a sintered glass filter of porosity 0 through liquid halothane contained in a 500-ml round-bottomed flask. Assuming that the mixture was saturated at the temperature of the liquid halothane (which was kept near 0 °C by an iced-water jacket), the concentration could be determined from the vapour-pressure formula* supplied by Imperial Chemical Industries Ltd. (Seiflow, 1961, personal communication) and a knowledge of the atmospheric pressure. Careful tests showed that the systematic errors introduced by uncertainty over the halothane temperature, by the mixture's being not quite saturated with halothane and by the non-linearity in the response of the katharometer (including the indicating galvanometer) were unlikely to exceed 5 per cent of the true value. In use the "reference" gas was about 1.5 per cent halothane in oxygen (in the inspiratory sample) instead of pure oxygen but this makes only a trivial difference in the sensitivity.

\[ \log_{10} p = 6.8468 - \frac{1079.74}{t + 222.06} \] where

\( p \) = pressure in mm Hg and \( t \) = temperature in °C.

Downloaded from https://academic.oup.com/bja/article-abstract/34/1/11/301354 by guest
on 29 December 2017
The following corrections were applied to the readings:

1. The rate of uptake is strictly equal to the difference between inspired and mixed-expired concentrations multiplied by the total ventilation only if the total mass of gases expired in a given time is the same as the total inspired. In fact oxygen and halothane are absorbed by the body, and carbon dioxide, water vapour and nitrogen are released. Carbon dioxide was absorbed in these experiments by soda lime and therefore need not be considered. Nitrogen excretion from the tissues is so slow (after the initial washout) that the error introduced by the resultant difference in total inspired and expired volumes is less than 1 per cent and can therefore be neglected. As for water vapour, although appreciable amounts are excreted, it can be shown that, since both sample streams were brought to nearly the same humidity as the gases used for calibration, no correction is necessary. The uptake of oxygen was assumed to be 200 ml/min (allowing for some depression of metabolic activity) and the uptake of halothane was found to be between 10 and 35 ml/min. Together these represented about 5 per cent of the average total ventilation (4.5 l./min). Therefore the effective volume of mixed gases expired in unit time was 5 per cent less than that inspired, and consequently the expired concentration of halothane was 5 per cent higher than it would have been with equal inspired and expired volumes. Accordingly the observed differences between the inspired and expired concentrations were increased by 5 per cent of the expired concentration.

2. The observed readings of the Dräger volumeter were corrected in accordance with a laboratory calibration made against a piston pump at various minute-ventilations.

3. In these experiments some halothane was taken up by the anaesthetic circuit as well as by the patient. This was due partly to a simple replacement of the oxygen initially in the circuit by the halothane mixture and partly to absorption of halothane by the rubber. This circuit uptake was determined in the laboratory in two dummy runs using a piston pump in place of the patient and an "inspired" concentration of 1.6 per cent halothane. The uptake observed in these runs was adjusted in proportion to the actual inspired concentration in each case in the theatre and subtracted from the values obtained for uptake by patient plus circuit. The correction became negligible (<1 ml/min) after 10 minutes.

Patients. Nine patients having elective surgery were studied (table I). The patients were in good health and showed no clinical evidence of cardiac or respiratory disease.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Operation</th>
<th>Sex</th>
<th>Age (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Femoral herniorrhaphy</td>
<td>F</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>Anterior colporrhaphy</td>
<td>F</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>Inguinal herniorrhaphy</td>
<td>M</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>Bilateral Trendelenburg and</td>
<td>F</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>stripping</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>Anterior and posterior col-</td>
<td>F</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>porrhaphy</td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>Subtotal thyroideectomy</td>
<td>F</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>Anterior and posterior col-</td>
<td>F</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>porrhaphy</td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>Dilatation and curettage</td>
<td>F</td>
<td>37</td>
</tr>
<tr>
<td>9</td>
<td>Excision of lump in breast</td>
<td>F</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>Means</td>
<td></td>
<td></td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>62</td>
</tr>
</tbody>
</table>

Anaesthetic procedure. For premedication the patients were given either 20 mg papaveretum and 0.4 mg hyoscine, or 10 mg morphine and 0.6 mg atropine. Anaesthesia was induced with thiopentone (150 to 300 mg). Suxamethonium (30 to 50 mg) was administered and the larynx and trachea were anaesthetized with 4 per cent lignocaine. A cuffed endotracheal tube was passed and connected to the experimental circuit.

At first oxygen alone was administered for about 3 minutes to wash out the nitrogen from the lungs. In a few patients there was some coughing and straining in this period but they quickly settled with further fractional doses of thiopentone. As soon as nitrogen washout was complete (as indicated by the katharometer reading zero) and the patient was breathing spontaneously, the Fluotec was turned to the chosen setting, between 1.2 and 1.7 per cent, and then left unaltered throughout the operation. If the resultant anaesthesia was inadequate it was augmented with intravenous Pethilorfan.

Readings of the katharometer and of the volumeter were noted at 1-minute intervals. The respiratory rate was measured less frequently.
RESULTS

For each patient the rate of uptake was calculated for each minute for which observations were made. There was a good deal of rapid fluctuation which could largely be attributed to fluctuations in ventilation, so 5-minute means of the rate of uptake were calculated and the results are listed in Table II.

According to Kety's (1951) theory of inert-gas exchange, rate of uptake is proportional to inspired concentration; and since Duncan and Raventós (1959) have failed to detect any metabolic products of halothane it may be regarded as biologically inert. Therefore it is reasonable to calculate the rate of uptake in terms of the volume of vapour taken up per minute for each per cent inspired concentration (ml/min per %). Then a mean value can be determined for all the patients for each 5-minute time interval. This has been done and the results are shown in figure 2. The vertical lines cover a range of plus or minus one standard deviation about the mean. This means that about two-thirds of the patients have rates of uptake which fall within this range. (No standard deviation can be indicated for the points beyond 90 minutes because they are derived from only one case—see Table II).

DISCUSSION

Scatter in the experimental results. The range of individual rates of uptake shown in figure 2 is substantial and a considerable part of it must be attributed to physiological differences between the patients. The only physiological variables that were measured were the body weight and the total ventilation (from which the alveolar ventilation could be estimated—see Appendix). However,
Kety's (1951) theory of inert gas exchange does not predict any close correlation between rate of uptake and body weight—and none was found. Also, although the theory predicts some correlation between the rate of uptake at the start and the alveolar ventilation—and some was indeed found—the correlation rapidly diminishes with time. In addition the experimental situation is complicated by the substantial fluctuations in alveolar ventilation which occurred in all patients. Therefore, although a large part of the scatter of the observations can be attributed to differences of alveolar ventilation it is not possible to take account of this in any systematic way.

Comparison of experimental results with theory. It is interesting to compare the mean experimental values of the rate of uptake of halothane vapour with those to be expected on the basis of theories of inert-gas exchange.

Kety's (1951) theory gives an equation (no. 55 in his paper) for the variation of alveolar concentration with time. It is based on the assumption that the tension of gas or vapour in arterial blood is in equilibrium with the tension in the alveoli, that the tension in mixed-venous blood is in equilibrium with the tension in the body tissues, and that the tissue/blood partition coefficient is unity. Since the rate of uptake is equal to the difference between inspired and alveolar concentrations multiplied by the alveolar ventilation (see Appendix) it is possible to derive from Kety's equation an expression for the rate of uptake. This has the form

\[ \text{Rate of uptake} = \dot{V}_A F_t \left( A_1 e^{-k_1 t} + A_2 e^{-k_2 t} \right) \]

where \( \dot{V}_A = \) alveolar ventilation, \( F_t = \) fractional inspired concentration, \( t = \) time, and \( A_1, A_2, k_1, \) and \( k_2 \) are functions of various physiological parameters of the body and physical properties of the anaesthetic.

Values have been allotted to these parameters as follows:

- Alveolar ventilation = 2.3 l./min. (Mean for the nine patients.)
- Body volume = 62 l. (This is numerically equal to the mean body weight of the patients in kg.)
- Cardiac output = 4.7 l./min.† (The cardiac index at the mean age of the patients (55) is 2.8 l/min × sq.m (Brandfonbrener, Landowne and Shock, 1955). Therefore cardiac output = 2.8 × 1.67 = 4.7 l./min.)
- Volume of gas in the lungs at midinspiration = say, 2.5 l. (This is not a critical factor in the equation and is not worth estimating closely.)

Inspired concentration = 1 per cent.

Blood/gas partition coefficient for halothane = 3.6 (Duncan and Raventós, 1959).

The equation has been solved for these values and in figure 3 the results, as shown by the broken curve, are compared with the experimental values. (Note that here the vertical lines indicate a range of plus or minus twice the standard error of the experimental mean; this means that for a large number of similar patients there is about a 95 per cent probability that the mean rate of uptake would fall within this range.) It can be seen that the calculated values are roughly in agreement with the observed values on the average but that the shape of the calculated curve is not right: in the first 60 minutes the calculated values are too high; while after 90 minutes they are too low.

Severinghaus (1954) in studying the rate of uptake of nitrous oxide, and Sechzer, Dripps and Price (1959) in studying cyclopropane, found a similar discrepancy between their results and the values calculated according to Kety's equation. (Sechzer, Dripps and Price worked in terms of the variation of expired concentration with time and not the actual rate of uptake but the same factors are involved.) Sechzer, Dripps and Price sought to explain the discrepancy by suggesting that the cyclopropane was not immediately distributed throughout the whole body but only over a part of it. They then calculated the “apparent distribution volume” at various times and found that this gradually increased during the administration.

However, it is possible to study this problem in a more systematic way. The assumption, involved in the derivation of Kety's equation 55, that the tension of anaesthetic in mixed venous blood is

\[ *This \text{ equation includes the anaesthetic stored in the lungs and therefore differs from the one derived by Severinghaus (1954) which took account only of the anaesthetic stored in the tissues.} \]

†The normal height for a weight of 62 kg is 165 cm (Documenta Geigy Scientific Tables). Therefore the most probable body surface area is 1.67 sq.m (from the Dubois nomogram).
in equilibrium with the mean tension in all the tissues, would only be valid if the blood flow per unit volume of tissue were the same throughout the body. Copperman (quoted by Kety, 1951) proposed a more comprehensive model of the circulation in which the body is imagined to be divided into a number of compartments such that the blood flow per unit volume of tissue is substantially the same throughout any one compartment but may differ widely in different compartments. He then derived an expression for the way in which the alveolar concentration varies with time. However, the evaluation of this expression involves a prodigious amount of arithmetic. Price et al. (1960) have proposed a similar model for predicting the redistribution of an intravenous injection of thiopentone. They did not derive any general equations for the concentration at any point; instead they wrote down the basic differential equations controlling the redistribution of the drug and solved them on a large electronic digital computer. However, it is possible to make a very simple electrical analogue of the physiological models of Copperman or Price et al. and to use it to compute factors involved in the distribution of anaesthetics, including the factor of rate of uptake.

Such a computer was constructed on lines similar to those independently suggested by Nunn (1960). It will be described separately. It has been used to determine the mean rate of uptake to be expected for the present nine patients, using the same values for alveolar ventilation, cardiac output, and so on as were used to solve Kety's equation. The way in which the total body volume and total cardiac output were assumed to be distributed amongst the various compartments was based on a fresh review of the literature which led to slightly different values from those used by Price et al. (1960).

The results of the computations are given by the continuous curve in figure 3. It will be seen that this curve is much closer to the observed values than the curve obtained from Kety's theory. Indeed, only in a few instances does the computed curve deviate from the observed means by more than twice the standard error of the mean.

Estimation of the rate of uptake in other patients. It should be remembered that the values shown in figures 2 and 3 apply to the particular nine patients studied, and that these patients had rather a high average age (55), and therefore probably had a rather low cardiac output (Brandfonbrener, Landowne and Shock, 1955). Also they had a low alveolar ventilation (mean 2.3 l./min) and their mean weight was only 62 kg. All these factors would tend to keep down the rate of uptake which might therefore be higher in larger, younger patients, particularly if their respiration were more active.

Since the computed values agreed so well with the experimental values for the nine patients studied it seemed legitimate to use the computer to estimate the rate of uptake that might occur with a younger patient with less depressed respiration. Accordingly the computer was "programmed" for a 70-kg man of surface area 1.83 sq.m, of age 20 to 29 (and therefore with an estimated cardiac output of 6.8 l./min according to Brandfonbrener, Landowne and Shock, 1955) and with the alveolar ventilation set firstly to 2.3 l./min as before, and secondly to 4 l./min. The results are shown in figure 4: the dotted
curve is for the alveolar ventilation of 2.3 l./min and the dashed and dotted curve for 4 l./min. It will be seen that the results are higher than for the nine patients studied experimentally (continuous curve) particularly when the alveolar ventilation is increased.

**Rate of uptake per % alveolar concentration.** From the point of view of estimating the concentrations of halothane inspired from a closed anaesthetic circuit (Mapleson, 1960), it is the rate of uptake per % alveolar concentration which is of importance. Therefore all the information in figures 3 and 4 (except the Kety curve) has been converted into this form (see Appendix) and replotted in figure 5. (For the experimental data, values were calculated for each minute for which observations were made for each patient and the means and standard errors calculated as for the rate of uptake per % inspired concentration). It will be seen that the computed values for the nine patients (continuous curve) are again in good agreement with the experimental values. Also the theoretical values for the young 70-kg patient again exceed those for the nine patients studied experimentally; but here the excess is less when the alveolar ventilation is 4 l./min (dashed and dotted curve) than when it is 2.3 l./min (dotted curve). This is because the effect of the increase in alveolar ventilation in increasing the rate of uptake (for a given inspired concentration) is more than compensated by its effect in increasing the alveolar concentration.

In 1960 a figure of 15 ml/min per % alveolar concentration was given by Mapleson as typical of the rate of uptake in the period from 20 minutes to 2 hours after induction. This was given before the various corrections mentioned in the "Method" section of this paper were made; now it appears from figure 5 that a value nearer to 20
ml/min per % alveolar concentration would be more typical of the nine patients studied but that the value would not be much higher in other patients with larger cardiac outputs or ventilations.

**SUMMARY**

The rate of uptake of halothane vapour in man has been measured in nine patients for periods up to 2 hours. The rate of uptake is high at the start, declines rapidly at first and then more and more slowly. In the period from 20 minutes to 2 hours after induction the average rate of uptake in these patients was of the order of 10 ml of halothane vapour per minute for each per cent inspired concentration, or 15 to 20 ml/min for each per cent alveolar concentration.

The theoretical values for the rate of uptake according to the theory of Kety as extended by Copperman have been calculated by means of a simple electronic analogue computer and the results have generally agreed with the experimental values to within plus or minus twice the standard error of the experimental means.

**APPENDIX**

**Determination of rate of uptake per unit alveolar concentration.**

The rate of uptake of anaesthetic, $\dot{V}_{p.a}$, is equal not only to the total ventilation multiplied by the difference between inspired and mixed-expired concentrations, but also to the alveolar ventilation, $\dot{V}_A$, multiplied by the difference between the inspired concentration, $F_A$, and the alveolar concentration, $F_A$. That is

$$\dot{V}_{p.a} = \dot{V}_A (F_I - F_A) \quad (1)$$

If $F_A$ is taken to be the fractional concentration of halothane with which arterial blood is in equilibrium, rather than the end-tidal concentration, then $\dot{V}_A$ will be that part of the ventilation which leaves the lungs in equilibrium with the arterial blood so far as its tension of halothane is concerned (the remainder of the ventilation being assumed to leave the lungs with the same tension of halothane as when it was inspired). Further, if it is assumed that the approach to equilibrium between blood and gas in the lungs in the case of halothane is as near as it is in the case of carbon dioxide then it follows that $\dot{V}_A$ is also that part of the ventilation which leaves the lungs in equilibrium with arterial blood so far as its tension of carbon dioxide is concerned. The value of $\dot{V}_A$, according to this definition, has been studied in anesthetized patients by Nunn and Hill (1960). The following formula for $\dot{V}_A$ can be deduced from their results and from their version of the Bohr formula

$$\dot{V}_A = 0.7\dot{V} - fV_D$$

where $\dot{V}$ is the total ventilation, $f$ the respiratory frequency and $V_D$ all the deadspace above a point 5 to 7 cm above the carina—in this work the internal volume of the apparatus from the Y-piece to the bottom of the endotracheal tube: 40 ml.

Equation (1) can be rearranged

$$F_A = F_I - \dot{V}_{p.a}/\dot{V}_A$$

and all the terms on the right-hand side can now be determined. The rate of uptake per unit alveolar concentration is $\dot{V}_{p.a}/\dot{V}_A$.

**ACKNOWLEDGMENTS**

A study of this nature could not be undertaken by a physicist alone and it is a pleasure to acknowledge the great help, so freely given, firstly, of Professor William W. Mushin whose guidance was so valuable in the planning, execution and analysis of this study, and, secondly, of Dr. S. Galloon who joined in the work so enthusiastically and made most of the measurements on patients. It is only their great modesty which prevents them from joining in authorship. Of almost equal importance was the help given by E. K. Hillard, Esq., Senior Technician to this department, in constructing apparatus. My grateful thanks are also due to Imperial Chemical Industries Ltd., for generous supplies of Fluothane and to their scientific staff for data about its properties.

**REFERENCES**


