Uptake of Methoxyflurane in Man at Constant Alveolar and at Constant Inspired Concentration

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Methoxyflurane uptake in man was determined both at constant inspired concentration (0.75 per cent) and at constant alveolar concentration (0.3 per cent). Uptake at constant inspired concentration was relatively constant falling from an initial value of 40 ml. per minute to a final value of 27 ml. per minute after 100 minutes. Conversely, uptake at constant alveolar concentration began at a still higher level but rapidly fell below uptake at constant inspired concentration. Initially, uptake was 65 ml. per minute. This fell to 30 ml. at 20 minutes and 19 ml. at 100 minutes. Despite the apparent smallness of these figures, they indicate removal of a large proportion of inspired anesthetic. In fact so much is removed during induction that it is physically difficult to produce inspired concentrations sufficient to attain or maintain anesthesia. It is particularly difficult to produce adequate concentrations with out-of-circuit as opposed to in-circuit vaporizers.

The rational use of any anesthetic agent is dependent on a knowledge of the uptake of that agent. A crude estimation of uptake may be gained by clinical observation of the required anesthetic input, but a more exact definition can be made only by actual measurement.

The reported high solubility of methoxyflurane (Penthrane) in blood (the blood/gas coefficient is 13) and other tissues would indicate that the uptake should be similar to that of diethyl ether (blood/gas coefficient of 12.1). As with any highly soluble gas, the uptake at a constant inspired tension should be considerably different from that at a constant alveolar tension. To determine the exact course of methoxyflurane uptake under either circumstance, the following experiments were performed.

Method

Eleven healthy patients (average age 37) who were to undergo various operative procedures were premedicated with 1.0 to 1.2 mg. atropine plus 100 to 250 mg. pentobarbital. Anesthesia was induced with 200 to 550 mg. (average 350 mg.) thiopental. Following relaxation with succinylcholine, the trachea was sprayed with cocaine (100 to 150 mg.) and intubated. Immobility was facilitated during the experimental observations with a continuous succinylcholine drip. The endotracheal tube was connected to a non-rebreathing system as diagrammed in figure 1. Inspired \( F_i \) and end-tidal \( F_e \) methoxyflurane 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 crossover effects of these gases on methoxyflurane analysis. Both expired and inspired samples read zero on the methoxyflurane meter when pure oxygen was respired. The analyzer was calibrated with samples of known methoxyflurane in the following manner.

Because of the low vapor pressure of methoxyflurane, it was not practical to make reference tanks. Instead aliquots of liquid methoxyflurane were injected into flasks of known volume (about 2,100 ml.) which contained a few drops of water. The percentage methoxyflurane vapor was calculated from the specific gravity (SG) of liquid methoxyflurane, the volume injected, the barometric pressure, and the ambient temperature as: (100 × volume of aliquot × SG of methoxyflurane injected × 22.4 × ambient temperature × 760)/molecular weight of methoxyflurane × 273 × barometric pressure × total flask volume). Aliquots of 0.025, 0.05, 0.1, 15, and 0.2 ml. were used so that full scale was approximately

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Methoxyflurane (Penthrane) for this study was donated by Abbott Laboratories.
2 per cent methoxyflurane. The instrument was calibrated in this fashion before and after each study.

Methoxyflurane-oxygen administration was begun 5 to 15 minutes after the last dose of thiopental. End-tidal gas was obtained by drawing samples at end-expiration from the patient end of a 30 ml dead space interposed between the endotracheal tube and non-rebreathing valve. The reservoir served to prevent contamination of end-tidal gas. 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 average, 20 minutes after the start of methoxyflurane administration. In five patients, the inspired methoxyflurane concentration was held constant at about 0.75 per cent (mean value) and the end-tidal concentration allowed to vary. In the remaining six patients, the end-tidal concentration was held constant at about 0.3 per cent (mean value) by adjustment of inspired concentration. These concentrations produced a maximum reduction of 20 mm. of mercury (mean systolic pressure) and 10 mm. of mercury (mean diastolic pressure) from the lowest pressure obtained before anesthesia.

Ventilation was controlled through a Ventimeter with a constant pressure ventilator. Tidal volume was determined at intervals by observation of volume change during inspiration with inflow 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 610 ml. with a mean rate of 16 breaths per minute. Alveolar tidal volume was estimated as tidal volume times 0.745. Alveolar minute volume was obtained by multiplying alveolar tidal volume by rate. Intermittently, the tidal volume was doubled or tripled to minimize atelectasis.

Methoxyflurane uptake per minute was determined as (inspired concentration minus end-tidal concentration) \times (alveolar minute volume). Uptake obtained was corrected to uptake per 70 kg. by multiplying by 70 kg./patient's weight. In the five patients in whom uptake was measured at a constant inspired concentration, a correction of 0.75/inspired concentration was made so that the concentration would be at an identical level for all calculations. The true mean figure was 0.75 per cent with a range of 0.72 to 0.80. A similar correction factor of 0.30 to 0.030 alveolar concentration was applied to the uptake figures from the six cases where the alveolar tension was held constant. The true mean figure was 0.30 per cent with a range of 0.02 to 0.32. This concentration was selected because in all cases except one it was sufficient to produce surgical anesthesia without requiring supplementation other than the inducing dose of thiopental. In addition, it was sufficiently low so that cardiovascular depression was not significant. No correction was made for water vapor or volume change.
TABLE 1. Data for Mathematical Model on Uptake and Distribution of Methoxyflurane at a Constant Alveolar Tension

<table>
<thead>
<tr>
<th>Tissue Group</th>
<th>Total Volume (liters)</th>
<th>Perfusion (liters/minute)</th>
<th>Tissue/Blood Partition Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRG</td>
<td>6.0</td>
<td>4.5</td>
<td>2.00</td>
</tr>
<tr>
<td>MG</td>
<td>33.0</td>
<td>1.1</td>
<td>1.34</td>
</tr>
<tr>
<td>FG</td>
<td>14.5</td>
<td>0.32</td>
<td>38.5</td>
</tr>
<tr>
<td>VPG</td>
<td>12.5</td>
<td>0.09</td>
<td>1.0</td>
</tr>
</tbody>
</table>

VRG: vessel rich group (brain, heart, kidney, hepatoportal system); MG: muscle group; FG: fat group; VPG: vessel poor group (bone, cartilage, ligament, tendon).

due to agent uptake, these being relatively minor factors.

The experimental data obtained at constant alveolar concentration were compared with data obtained from a previously described mathematical model. This model assumes a constant arterial (alveolar) tension. Tissue flow is divided between four groups whose properties are outlined in Table 1. Cumulative uptake for any tissue group is obtained as $V_{GT} = K_1 (1 - e^{-K_2 T})$ where $V_{GT}$ is the volume of methoxyflurane in the tissues at time $T$, and $K_1$ is a constant equaling the tissue/blood partition coefficient times volume of the tissue times the arterial methoxyflurane concentration. Arterial concentration is calculated as the blood/gas partition coefficient of 13 times 0.003. $K_2$ is a constant equaling blood flow per unit volume of tissue divided by the tissue/blood partition coefficient. Uptake during any given minute is obtained by subtracting the sum of the $V_{GT}$'s at the start of the minute from the sum at the end.

From the calculated data on uptake, one may calculate the inspired concentration required to maintain the alveolar concentration constant at 0.3 per cent. Varying alveolar ventilation ($V_A$) varies the required inspired concentration.

Similarly, one may predict the methoxyflurane concentration in the gas flowing into a rebreathing system required to hold the alveolar concentration at 0.3 per cent. In this case, both alveolar ventilation and inflow rate must be known. The calculations used do not allow for washout of the rebreathing system, but rather, at each point of time, assume a temporary balance between uptake, alveolar concentration, circle concentration, and inflow concentration. The actual equations used are similar to those developed by Mapleson.

Results and Discussion

Figure 2 shows the difference between methoxyflurane uptake at a constant inspired concentration and uptake at a constant alveolar concentration. When the inspired concentration is held at 0.75 per cent, uptake begins at a high of about 40 ml. during the first minute, decreases to about 30 ml. per minute at 20 minutes, and falls only slightly thereafter. After 100 minutes of anesthesia, uptake is still 27 ml. per minute. This is in contrast to what is found at a constant alveolar

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Fig. 2. A comparison of methoxyflurane uptake per 70 kg. at constant inspired concentration of 0.75 per cent (open circles and broken line) and at constant alveolar concentration of 0.3 per cent (closed triangles and continuous thin line). The heavy continuous line represents theoretical uptake (four compartment model) by a 70 kg. man when the alveolar concentration equals 0.3 per cent. Other parameters are described in Table 1.
concentration of 0.30 per cent. Here uptake is 65 ml in the first minute; falls to less than half this after 20 minutes; and at 100 minutes is further reduced to 19 ml per minute. These differences between the two techniques (constant alveolar versus constant inspired) are similar to those found for halothane in a previous study. They may be anticipated for any anesthetic having an appreciable blood solubility. The flat uptake curve seen with a constant inspired mixture occurs because as the tissues become saturated at one alveolar (arterial) tension, the tension is free to rise further since it is far below that inspired. The increase in alveolar tension maintains the tension gradient from arterial blood to tissue and hence maintains uptake. Contrariwise, as tissues become saturated at a constant alveolar tension, there is no compensatory rise in alveolar tension. Hence, uptake continues to fall as more and more tissues equilibrate with the arterial concentration.

For the most part, the experimental and theoretical graphs for uptake at a constant alveolar concentration are reasonably close. Minor discrepancies are seen which are in part related to the variation found in any in vivo study. They are also partly related to the limitations of the study. For example, in four of the six subjects, it took three to five minutes to reach 0.3 per cent alveolar concentrations. During the first three minutes, then, uptake is underestimated and this explains the relatively low values seen at this time. The initial period of the study (the first 20 to 40 minutes) was also the period of the most pronounced fall in blood pressure. Although the fall was not considered to be hazardous to the patient, it probably reflected a decrease in cardiac output. This would explain the slightly lower uptake relative to the theoretical graph during this time. With the onset of surgery, the blood pressure usually rose. Assuming a concomitant rise in cardiac output, uptake relative to the predicted curve should and does increase after this time. One theoretical possibility which might cause an underestimate of uptake is inherent in the high solubility of methoxyflurane in tissues and in rubber. During inspiration the tracheobronchial tree and endotracheal tube are exposed to and partially equilibrate with the inspired concentration.

Because of its high solubility in these areas, the methoxyflurane in them may not be completely "washed out" by the initial portion of the egressing alveolar gas. If these areas continue to contribute methoxyflurane during all phases of expiration, this would raise the apparent alveolar concentration and may reduce the calculated uptake. Such a possibility is supported by the work of Cander and Forster with highly soluble vapors such as ether and acetone.

If alveolar anesthetic concentration equals brain concentration, then a constant alveolar concentration reflects a relatively constant level of anesthesia. The above figures, therefore, provide a guide to the average amount of methoxyflurane required to maintain a stable light level of anesthesia. The inspired methoxyflurane concentration required to maintain this level may be predicted (Fig. 3) from the uptake figures given by the theoretical curve. The graphs of required inspired concentration
have the same shape as the uptake curve from which they are derived. A relatively high but rapidly decreasing concentration is initially found. This falls to a knee between 10 and 20 minutes after which the fall continues but at a much slower rate. The required concentration varies inversely with ventilation: the lower the alveolar minute volume, the greater the required percentage. At 30 minutes, for example, when $V_A$ equals 2 liters per minute, the inspired concentration must be 2.08 per cent; but when $V_A$ is 4 liters per minute, the required inspired concentration falls to 1.19 per cent. At a $V_A$ of 8 liters per minute, the concentration is further reduced to 0.74 per cent. Clinically, then, if ventilation is altered, the administered concentration must be correspondingly adjusted. For example, the increase in ventilation on changing from spontaneous to controlled ventilation would require a decreased methoxyflurane input.

At the lower alveolar ventilations of 2 and 4 liters per minute, the requirement initially exceeds the vapor pressure of methoxyflurane (about 4 per cent at room temperature). Thus, when $V_A$ is 2 liters per minute for the first six to seven minutes, it is impossible to deliver adequate concentrations. At $V_A$ equals 4 liters per minute, adequate concentrations may be obtained after two to three minutes. Even these time limits are for a non-rebreathing system in which all delivered gas is saturated with methoxyflurane.

The problem of delivery of an adequate vapor tension becomes even greater when a rebreathing system is interposed between the methoxyflurane vapor source and the patient. If alveolar ventilation is held constant at 4 liters per minute, the inflow concentrations required to maintain alveolar concentration at 0.3 per cent are illustrated in figure 4. Again, the curves are similar in shape to the uptake curve with a rapid initial fall to a knee after which the fall continues but at a slower rate. At one liter per minute inflow, the required concentration initially is 20 per cent. After five minutes at this inflow, it has fallen to 11 per cent; and after 20 minutes, it has fallen to 5.5 per cent. Only after 40 minutes does it fall to a concentration physically possible to deliver (4 per cent). Even at this time to achieve this concentration, all the inflowing gas must be directed through the vaporizer. At 2 liters per minute inflow, the situation improves somewhat; and it is possible to deliver an adequate concentration after 12 minutes (all inflow through the vaporizer). At 4 liters per minute inflow, the time drops to six minutes; and at 8 liters per minute inflow it drops to four minutes. This correlates well with the experience of Artusio et al. who found that at a flow of 3 liters per minute through the Copper Kettle, 12–14 minutes were required before intubation could be undertaken successfully. Few American anesthetic machines, however, are calibrated to deliver 4 to 8 liters per minute through the vaporizer. It is theoretically possible to do so with the Boyle’s machine although at these flows inadequate vaporization would probably occur.

For at least two reasons these graphs probably underestimate the required inflow concentration:

1. No attempt is made to determine the additional agent required to “wash out” the system initially.
(2) Uptake of methoxyflurane by rubber goods is not accounted for. At the lower inflow of 1 and 2 liters per minute, the rubber goods may remove from 20 to 50 per cent of the methoxyflurane introduced.6

It is apparent from the above that the out-of-circuit vaporizer may limit the rate of induction with methoxyflurane. The in-circuit vaporizer may be used to advantage with this agent since output of the vaporizer is dependent on minute volume. Inflow can be low. This limits the loss of agent to ambient air without reducing the concentration of agent presented to the patient.

The most commonly accepted solution to the problem of slow induction with methoxyflurane is to initiate anesthesia with a rapid acting agent such as nitrous oxide or thiopental.8-12 Methoxyflurane is then added as needed to supplement or replace the inducing agent.

The problem of recovery from methoxyflurane varies with the duration of anesthesia. If the duration is short, then recovery may be reasonably rapid since the blood tension is reduced both by loss through the alveoli and by redistribution to other tissues. Usually, however, methoxyflurane is used in long procedures so that considerable tissue saturation occurs. Redistribution, therefore, decreases in importance; and in fact, the tissues may act as a reservoir which sustains the arterial concentration. Under these circumstances a slow, prolonged recovery may be expected. This may be avoided in part through the use of methoxyflurane as an adjuvant to agents such as nitrous oxide which are rapidly eliminated. Under these circumstances—where methoxyflurane is used to "top" nitrous oxide—recovery to wakefulness may be rapid although incomplete. This may be advantageous if analgesia is desired in the immediate postoperative period.

Although the concentration of methoxyflurane in the inflowing or the administered mixture may be accurately controlled, the alveolar concentration may be subject to considerable variation. There is no rigid correlation between the percentage methoxyflurane administered and that found in the alveoli. The latter is also determined by inflow rate, by ventilation, and by uptake.

**Summary**

Methoxyflurane uptake at a constant inspired concentration of 0.75 per cent was determined in five healthy human beings. Uptake fell slowly with time from an initial high of 40 ml per minute, to 30 ml per minute at 20 minutes, and to 27 ml per minute at 100 minutes. Methoxyflurane uptake at a constant alveolar concentration of 0.3 per cent was also determined in six healthy human beings. Compared to the previous study, uptake fell rapidly with time. Initially, uptake equalled 66 ml per minute but fell to 30 ml per minute within 20 minutes. Uptake decreased slowly thereafter; and at 100 minutes, it equalled 19 ml per minute. This rate of uptake paralleled that predicted mathematically using a four-compartment model of the body.

The implications of the rate of uptake at a constant alveolar methoxyflurane concentration were noted to be the following: (1) Induction with an out-of-circuit vaporizer must be slow unless the inflow rate is high (8 liters per minute). The inflowing gas must be saturated with methoxyflurane. (2) A more rapid and economical induction may be achieved with an in-circuit vaporizer. (3) The anesthetic level may not be related solely to inflowing concentration in an anesthetic system: factors such as inflow rate, ventilation, and uptake are of equal importance.

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**References**

METHOXYPYFLURANE Saturation concentration of the vapor at 4 per cent in air at 25° C. limits the use of high initial concentrations for hastening the onset of anesthesia. Since the agent is highly soluble in blood and tissues, at least 8 minutes is required before anesthesia is obtained. A calibrated vaporizer is not necessary, particularly for short cases. Recovery is slow. Two main side effects are hypertension and respiratory depression. The cause of the fall in blood pressure has not been fully explained. The main effect on breathing is a reduction of tidal volume. Tachypnea is an indication of inadequate anesthesia. The metabolic effects of the drug have not been investigated. (Editorial: Methoxyflurane, Lancet 2: 446 (Aug. 31) 1963.)

POLYCYTHEMIA Postoperative complications occurred in 35 per cent of patients with polycythemia vera. Fifty-two per cent of these were due to hemorrhage; 18 per cent to thrombosis, and 14 per cent to hemorrhage and thrombosis in the same patient. There was an 18 per cent postoperative mortality which is significantly higher than the expected percentage in otherwise normal subjects. When polycythemia was not controlled prior to surgery, the incidence of complications was 83 per cent; when controlled, 21 per cent. The longer the effective control period prior to surgery, the lower the complication rate. The recommendation is made that elective procedures should be avoided or delayed until adequate control is achieved. The treatment must be directed at a reduction in the red cell mass and also at the thromboeytosis that may follow spontaneous bleeding or phlebotomy. When possible phlebotomy should be followed by the administration of myelosuppressive agents for a period necessary to achieve and maintain a normal blood count. Otherwise, the red blood cell mass should be reduced to normal by repeated phlebotomies. (Wasserman, L. R., and Gilbert, H. S.: Surgery in Polycythemia Vera, New Engl. J. Med. 269: 1226 (Dec. 5) 1963.)