Recent evidence has suggested that the rate of uptake of inhalational anaesthetic is constant during maintenance of anaesthesia, contrary to the predictions of multi-compartment uptake models. We measured isoflurane uptake using a totally closed anaesthetic system during up to 10 h of stable anaesthesia for maxillo-facial surgery on 12 adult patients. Liquid isoflurane was injected into the system under computer control to produce an end tidal concentration of 1.3 MAC of isoflurane. Bench tests demonstrated that the leakage from the system was less than 8 μl min⁻¹, confirming that the rate of injection of isoflurane into the system was a close upper bound on the patients’ uptake. Anaesthetic usage for a 70 kg patient was 0.44±0.51t+0.044t-0.013t+0.058t-0.00098t ml min⁻¹ of liquid isoflurane, where t is duration of anaesthesia in minutes. There was a continuing reduction in anaesthetic requirement even at the end of the period of study that was statistically significant. These data do not support the notion that isoflurane uptake is constant during stable maintenance of anaesthesia but is compatible with the conventional multi-compartment model of anaesthetic uptake and distribution.

**Keywords:** induction, anaesthesia; model, compartmental; anaesthetic techniques, inhalation; pharmacokinetics, isoflurane

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The uptake of inhalational anaesthetic agents by the body is a subject of both practical and theoretical interest. During induction, an anaesthetizing partial pressure is achieved rapidly at the well-perfused site of action in the brain, but to maintain this partial pressure, anaesthetic must be continuously supplied to meet uptake elsewhere in the body. The total load of anaesthetic is a major factor determining the amount of metabolism and the formation of possibly toxic metabolites. The multi-compartment model of anaesthetic uptake and distribution has been promulgated for many years¹ ² and has much experimental evidence to support it.²⁻⁷ The model represents the human body by a few compartments, each of homogeneous composition and perfusion. Anaesthetic is assumed to accumulate in each compartment at a rate proportional to its perfusion, the partial pressure difference between arterial blood and the compartment, and the solubility of the gas in that compartment. Measurements of the graded manner in which uptake proceeds (i.e. the shape of the uptake curve), provide evidence of the physical factors responsible for the distribution of anaesthetic in the body.

The multi-compartment model has never been accepted universally,⁸ and recent work has been interpreted as evidence that anaesthetic uptake is constant after the first few minutes of inhalational anaesthesia.⁹ We have investigated this controversy by measuring the uptake of isoflurane during prolonged anaesthesia. We studied 20 patients undergoing reconstructive head and neck surgery using a computer-controlled closed anaesthetic breathing system into which isoflurane was injected to maintain a concentration of 1.3 MAC.

**Methods**

**The breathing system**

The apparatus used was a functionally closed breathing system, delivering oxygen automatically via a ‘gas piston’.¹⁰¹¹ Mechanical ventilation is transmitted from the Y-connector of an Ohmeda 7900 ventilator (Ohmeda, Madison, USA) to the breathing system by a volume of gas acting as a piston in a 6 m ‘trunk’ of 22 mm corrugated plastic tube. There is no conventional fresh gas supply to this system, but some of the oxygen oscillating in the trunk is retained in the circle as oxygen there is consumed by the patient.¹² Liquid isoflurane is injected directly from a glass
syringe (GT-50, SGE Europe Ltd, Milton Keynes, UK) into an in-circle vaporizing chamber (Fig. 1). The concentration of isoflurane within the system is measured by a Capnomac (Datex, Helsinki) multi-gas analyser, which was calibrated before use. The sampled gas is returned to the breathing system. A computer communicates with both this analyser and the isoflurane syringe pump, and controls the rate of isoflurane injection to achieve and maintain a predetermined end-expired concentration.

**Bench test**

Anaesthetic loss from the breathing system was measured using a model lung. The model lung consisted of a 22.2 litre glass bottle with a tracheal tube inserted through its stopper. To prevent any absorption of volatile anaesthetics, the internal surface of the bung was covered with aluminum foil and the exterior of the assembly was covered with a silicone sealant. The model lung was attached to the breathing system in place of a patient. The system was ventilated with a tidal volume of 650 ml at a rate of 10 min⁻¹, producing a peak pressure of 25 cm H₂O. Isoflurane was injected into the vaporizing chamber as described above, until its concentration in the circuit reached 3%. The injection pump was then stopped and an estimate of the rate of anaesthetic loss from the system was calculated from the wash-out curve. This is the obligatory loss, and is less than we expect to occur clinically.

**Conduct of anaesthesia**

After Ethics Committee approval and informed consent had been obtained, 20 patients undergoing head and neck surgery, were studied. A multi-disciplinary team of maxillo-facial, ENT, and plastic surgeons were involved to undertake these lengthy surgical procedures, some of which lasted up to 18 h. The surgery involved excision of tumour and reconstruction of the defect with a free tissue flap. The patients received oral temazepam premedication. Anaesthesia was induced with propofol 2.5 mg kg⁻¹ and fentanyl 4 μg kg⁻¹. A laryngeal mask airway (LMA) was then inserted, the patients were connected to a closed breathing system, and controlled ventilation was instituted. Liquid isoflurane was injected as described above to achieve and maintain an end-expired concentration of 1.5%. The airway was then secured by percutaneous dilatational tracheostomy. Atracurium (0.5 mg kg⁻¹) was used to facilitate insertion of the tracheostomy tube; no further dose of muscle relaxant was administered. The closed breathing system was then disconnected from the laryngeal mask and connected to the cuffed tracheostomy tube. Anaesthesia was continued with 1.5% end-expired isoflurane and an infusion of fentanyl at 0–5 μg kg⁻¹ h⁻¹. The end-expired carbon dioxide was maintained at 4.5 kPa.

Arterial and central venous catheters were placed using the radial artery and femoral vein respectively. ECG, arterial blood pressure, urine output, temperature (core and peripheral), haemoglobin and haematocrit, arterial blood acid-base status, fluid intake, and blood loss were monitored throughout. Temperature was maintained by surface warming (Bair Hugger, Eden Prairie, MN, USA). During the first 30 min of anaesthesia, it was occasionally necessary to treat hypotensive episodes with a 3-mg bolus of ephedrine. Thereafter, satisfactory blood pressure was maintained by infusion of i.v. fluid at 6–8 ml kg⁻¹ h⁻¹, using Hartmann’s solution and Gelofusine (Braun, ²LMA is the property of Intavent Limited.

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1. Fig 1 The breathing system. There is no conventional fresh gas flow oxygen being drawn up the trunk to replace volume lost from the breathing system from oxygen consumption. The anaesthetist sets the target end-expired isoflurane concentration on the computer, which then controls the rate of the syringe pump to achieve and maintain that value on the basis of measurements made by the gas analyser.
Melsungen, Germany) in a ratio of 4:1. Blood was given as required to maintain the haemoglobin concentration between 8 and 10 g dl\(^{-1}\). In closed systems the inspired oxygen fraction (\(F_{\text{IO}_2}\)) reduces as nitrogen accumulates as a result of: (i) wash-out from the patient\(^{14}\) and (ii) the addition of air from the Capnomac oxygen reference flow, which is added to the sample return flow at a rate of 24 ml min\(^{-1}\). \(F_{\text{IO}_2}\) was maintained above 0.3 by intermittently venting the sample returned from the Capnomac so that oxygen entered the system from the gas piston. Any leak in the system revealed itself by an increase in \(F_{\text{IO}_2}\) as oxygen from the gas piston replaced volume lost from the system.

**Data analysis**

The recorded rate of injection was normalized to 70 kg in proportion to each patient’s body weight. The patient results were too noisy to allow useful individual analysis. The parameters of the function \(\sum A_i e^{-k_i t}\) were adjusted to produce the best (i.e. least squares) simultaneous fit to the data, using an iterative technique on a spreadsheet (Solver, Microsoft Excel 97 SR-1). This function is the mathematical representation of exponential wash-in to multiple compartments. The significance of improvement in curve fit with increasing numbers of compartments was assessed using an F-ratio test.\(^{15}\) If these pharmacokinetic compartments are associated with the classical vessel rich, muscle and fat tissue groups, then compartment volumes and perfusions can be calculated. The amount of isoflurane in each compartment is given by integrating the appropriate term in the equation from zero to infinity. At 37°C the vapour volume of isoflurane is 207 times the liquid volume, and remembering that the equilibrium tissue concentration of isoflurane is 1.5\(\lambda_{TG}\)%, where \(\lambda_{TG}\) is the tissue:gas partition coefficient, we deduce that the volume of the \(i\)th compartment is 207 \(A_i/ (0.015 + \lambda_{TG})\) ml. The compartment perfusion is derived from the rate constant:

\[
k_i = q_i \lambda_{BG}/ \lambda_{TG},
\]

where \(\lambda_{BG}\) is the blood:gas partition coefficient for isoflurane and \(q\) is the perfusion in units of ml blood (ml tissue\(^{-1}\) min\(^{-1}\)) (see Table 2 for the values of partition coefficient used).

Simple linear regression was used to test the hypothesis that the rate of isoflurane uptake was continuing to reduce during the terminal period of our study (400–600 min).

**Results**

Patient characteristics are given in Table 1. The conduct of anaesthesia was satisfactory in all cases. Temperature was maintained at 37°C (core) and >35°C (peripheral). Urine output was between 2 and 2.5 ml kg\(^{-1}\) h\(^{-1}\). Blood loss was in the range of 1500–2000 ml. Three bench tests were carried out to measure leakage from the system using the artificial lung and leakage was found to be 3, 7, and 8 ml min\(^{-1}\) of liquid isoflurane.

The records of six patients were discarded from the series because of a failure of nitrogen accumulation indicated excessive leak from the system, most probably from the tracheostomy site. Records from two other patients were rejected because the target concentration was changed during anaesthesia. A full set of the data can be obtained from http://bja.oupjournals.org. The mean rate of decrease of oxygen concentration among the patients whose results are included in the analysis was 0.12% min\(^{-1}\) (minimum 0.05% min\(^{-1}\)). There was a clear correlation of isoflurane requirement with patient weight: at 3 h the cumulative uptake correlated significantly with weight \((n=11, r^2=0.76, P<0.0005)\). Figure 2 shows the rate of isoflurane injection, normalized for each patient by simple proportion to 70 kg, together with the number of patients contributing data at those times. The data were compatible with a three-compartment model. The line of best fit is shown in bold in Figure 2 and is given by \(0.44 e^{-0.51 t} + 0.044 e^{-0.013 t} + 0.058 e^{-0.00098 t}\) ml min\(^{-1}\) of liquid isoflurane for a 70 kg patient, where \(t\) is the duration of inhalational anaesthesia in min. The slope of the regression line through the last 200 min of weight-corrected data was significantly different from zero (95% CI from \(-0.00075\) to \(-0.00005\) ml min\(^{-2}\) liquid isoflurane). The regression line through individual data was also significantly less than zero \((P<0.005)\) for all but one patient—the soda lime was changed at 520 min in that case, distorting the data.

When a value of 8 ml min\(^{-1}\) or less was subtracted from every usage datum point to give an estimate of uptake, the changes were modest: \(0.44 e^{-0.51 t} + 0.043 e^{-0.013 t} + 0.051 e^{-0.0012 t}\) ml min\(^{-1}\) of liquid isoflurane for a 70 kg patient. The characteristics of the derived compartments are listed in Table 2.

**Discussion**

We have measured the rate of anaesthetic usage and, because the system is closed, we use it as an estimate of the rate of anaesthetic uptake. Our bench tests have shown a loss of up to 8 ml min\(^{-1}\) from a sealed model lung and we expect that leak around the airway will result in greater

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Duration (min)</th>
<th>Cumulative uptake (ml liquid isoflurane)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>at 3 h</td>
</tr>
<tr>
<td>45</td>
<td>70</td>
<td>298</td>
<td>16.0</td>
</tr>
<tr>
<td>36</td>
<td>118</td>
<td>&gt;600</td>
<td>25.7</td>
</tr>
<tr>
<td>45</td>
<td>69</td>
<td>&gt;600</td>
<td>16.8</td>
</tr>
<tr>
<td>25</td>
<td>80</td>
<td>288</td>
<td>16.2</td>
</tr>
<tr>
<td>49</td>
<td>70</td>
<td>159</td>
<td>(13.3)</td>
</tr>
<tr>
<td>42</td>
<td>60</td>
<td>&gt;600</td>
<td>8.7</td>
</tr>
<tr>
<td>50</td>
<td>69</td>
<td>&gt;600</td>
<td>12.1</td>
</tr>
<tr>
<td>73</td>
<td>58</td>
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<td>7.8</td>
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</tr>
<tr>
<td>44</td>
<td>86</td>
<td>290</td>
<td>13.6</td>
</tr>
</tbody>
</table>
losses in clinical use. There are additional leaks when the
airway is manipulated early in the procedure, when the
system is flushed and during changes of soda lime. We have
found no formal data-processing algorithm that allows for
these and have rejected the alternative approach of manual
adjustment of the data until it ‘looks right’. We prefer
instead to use our data to indicate what must be the upper
bounds on actual uptake. The additional losses tend to mask
a gradual reduction in anaesthetic requirement. We have
been able to demonstrate that a gradual decrease in uptake
occurs. Our results are important because of the long
duration of the measurements and the fact that we have been
generous in the inclusion of losses that work against our
significant result. Because these data can be analysed using
a variety of methods we have provided access to our original
data, so that other workers may inspect or use them.

Uptake by the patient does not necessarily imply
accumulation within the body. Losses of anaesthetic by
diffusion through skin,\textsuperscript{16} mucous membrane, from
wounds,\textsuperscript{17} urine, and metabolism\textsuperscript{18} should be insignificant.
Assuming the solubilities of isoflurane in urine and saline
are the same, the loss is approximately 9 ml of isoflurane
vapour per litre of urine, or 0.5 ml min\textsuperscript{−1} liquid isoflurane for
our patients. The isoflurane content of the blood loss would
have been an order of magnitude less. We are aware of only
one mechanism by which our results could underestimate
uptake. Methane can accumulate in closed breathing
systems and has been reported to cause a gas analyser
such as ours to read 0.79\% halothane spuriously during total
i.v. anaesthesia.\textsuperscript{19} The gain used in the infra-red system is
less when isoflurane is selected and so methane would cause
a lesser reading of 0.13\% with isoflurane.\textsuperscript{20} That could mean
that we were maintaining only 1.37\% isoflurane (the
remainder of the 1.5\% being a spurious contribution from
methane), resulting in a 9\% underestimate of anaesthetic
uptake at a true 1.5\% concentration.

Airway manipulation and temporary disconnections
of the breathing system resulted in very noisy data sets,
especially during the first 30 min of anaesthesia. It is
surprising that the mean uptake figures during this
period have such plausible values. These noisy data
detract less from the accuracy of our uptake measure-
ments later in the anaesthetic, which was the main focus
of this study.

\begin{table}
\centering
\begin{tabular}{llllllllll}
\hline
Data & VRG (\(\lambda_{T:G} 2.5\)) &  & Muscle group (\(\lambda_{T:G} 2.1\)) &  & Fat (\(\lambda_{T:G} 70.5\)) &  & C.O. (litres min\textsuperscript{−1}) \\ 
Volume (litres) & Perfusion (ml 100 ml\textsuperscript{−1} min\textsuperscript{−1}) &  & Volume (litres) & Perfusion (ml 100 ml\textsuperscript{−1} min\textsuperscript{−1}) &  & Volume (litres) & Perfusion (ml 100 ml\textsuperscript{−1} min\textsuperscript{−1}) &  \\ 
\hline
Usage & 4.8 & 91 & 23 & 1.9 & 12 & 4.9 & 5.3 \\ 
Uptake & 4.8 & 91 & 22 & 1.9 & 8.2 & 6.2 & 5.2 \\ 
\hline
\end{tabular}
\caption{Compartmental data derived from modelling, assuming the compartment solubilities shown in the first line and a blood:gas partition coefficient of 1.4. The rightmost columns show the cardiac output implied by the results. (Abbreviations: VRG, vessel rich group; \(\lambda_{T:G}\), isoflurane tissue:gas partition coefficient; C.O., cardiac output derived by summing compartmental blood flows)}
\end{table}
Our results show that anaesthetic uptake continues to reduce for 10 h. That may seem to run counter to a recent statement by Hendrickx and co-workers that uptake becomes effectively constant after a 4 min wash-in period. Lin too has claimed that uptake is constant. There are three reasons that make this contradiction more apparent than real. First, we agree with the editorial accompanying Hendrickx's work that his results show uptake reducing throughout the first 49 min, not constant from 4 min. Second, we have presented our results in terms of rate of uptake, not cumulative uptake. The small, continued reduction in rate of uptake would indeed become almost negligible when viewed atop the accumulated load of isoflurane. Finally, we have been careful to keep our breathing system as near completely closed as possible. A small but constant leak, as might occur in routine use, would require an increase in anaesthetic delivery to counter it, so the reduction in anaesthetic uptake would be a smaller part of the rate of anaesthetic use and therefore less easy to discern. Thus, although we can agree that, for clinical purposes, isoflurane uptake becomes almost constant after a period of wash-in, uptake actually continues to reduce over a period of at least 10 h. Our results are compatible with the conventional perfusion-limited model of anaesthetic uptake and distribution.

References