Quantitative study of Lowe’s square-root-of-time method of closed-system anaesthesia


Summary

Intermittent injection of liquid anaesthetic into a closed breathing system is particularly suitable in countries with limited resources. A method of calculating appropriate times and magnitudes of the injected doses was described by Lowe but the method has never been assessed rigorously. Such an assessment was the purpose of this study. The technique was used in a double-blind, randomized comparison of halothane, enflurane and isoflurane in oxygen–air, with 20 ASA I or II patients in each group, undergoing superficial or abdominal surgery. The prescribed times of injection were adhered to, but the doses, after the first two, were adjusted to maintain systolic arterial pressure within 20% of the reference preoperative value. Partial pressures of the anaesthetics were monitored but concealed from the investigator–anaesthetist. The mean doses found necessary for each anaesthetic were within 33% of those calculated to produce 1.3 MAC. However, end-tidal partial pressure (just before each dose) stabilized at a steady level of only 0.97, 0.42 and 0.77 MAC for halothane, enflurane and isoflurane, respectively. Recovery from enflurane was much more rapid than that from the other agents but no patient admitted to any dreams. We conclude that the rate of uptake of anaesthetic declines more slowly than predicted and that the patients receiving enflurane were less deeply anaesthetized because the greater hypotensive effect of enflurane led to the use of smaller doses. (Br. J. Anaesth. 1997; 79: 103–112).

Key words


Lowe,1 and subsequently Lowe and Ernst,2 have argued theoretically that if a “priming dose” of liquid anaesthetic is injected into a closed anaesthetic breathing system at 0 min, and a “unit dose” at 1, 2, 3 (1, 4, 9), etc. min, arterial partial pressure of the anaesthetic increases rapidly and then stays constant. Specifically, the priming dose should bring the gas in the breathing system and arterial blood to the specified partial pressure, often taken to be 1.3 MAC; subsequent unit doses should supply uptake to the tissues that occurs during the interval until the next dose. The argument is supported by calculations by Mapleson.3 It is acknowledged2 that different patients need different concentrations and therefore different doses, and that these are tailored to the patient by a competent anaesthetist. This technique of anaesthesia is particularly suitable for developing countries.

However, there are two gaps in our knowledge of the method. First, although a closely related method has been studied,4 the Lowe method has never been subjected to rigorous quantitative assessment. Second, when Couto da Silva and others5–8 used this method in unblinded studies with halothane, enflurane and isoflurane, they found that the injected volumes of enflurane required to maintain a constant systolic arterial pressure (SAP) were much less than the 1.3-MAC unit dose, and that recovery was more rapid with enflurane than with halothane or isoflurane. However, they could not identify the cause of the discrepancies because they were unable to measure anaesthetic partial pressure.

Therefore, this study was designed to answer four questions on the clinical use of Lowe’s method. (1) Are the required doses, and the resulting arterial partial pressures, consistent with Lowe’s theory? (2) Can the findings of Couto da Silva be replicated in a double-blind study? (3) If so, can the cause of the discrepancy between agents be elucidated? (4) Whatever the answer to these three questions, does Lowe’s method produce satisfactory anaesthesia?

Patients and methods

STUDY DESIGN

On the basis of an exploratory study,9 60 adult patients were allocated randomly by a computer program10 to be anaesthetized with halothane, enflurane or isoflurane (20 patients per group).

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Patient and anaesthetist were blinded to the agent used. Inclusion criteria were: ASA status I or II, age 20–65 yr, and upper or lower abdominal, or superficial surgery lasting at least 75 min. Exclusion criteria were: halothane anaesthesia within the previous 3 months; heavy intake of alcohol; cardiac, pulmonary, neurological or renal disease; patients receiving any drug that could alter the MAC of the anaesthetics; and pregnancy. Informed, verbal consent was obtained from all patients and the study was approved by the relevant local research Ethics Committee.

Patients were anaesthetized according to the square-root-of-time method, with a specified partial pressure of 1.3 MAC, and as practised in developing countries except as follows. To assist in blinding, the dose at 0 min was 2 ml for all three anaesthetics and that at 1 min was 1, 1.5 or 2 ml according to body weight (less than 60 kg, 60–75 kg and greater than 75 kg, respectively). These doses were justified by the exploratory study.9 The prescribed times of subsequent doses were adhered to, but the doses were chosen by the anaesthetist as those most likely to maintain or regain the required depth of anaesthesia. “Normal” depth was defined primarily as an SAP within 20% of a reference preoperative SAP, with some allowance for other clinical signs (heart rate, sweating, tears). The times from opening the breathing system to four stages of recovery were recorded and, on the day after operation, four questions were used to determine the patient’s memory and opinion of the anaesthetic (see below).

Monitoring additional to that required for the above was carried out, but all results for the critical variable, partial pressure of the anaesthetic, were concealed from the anaesthetist until the end of the study. End-tidal partial pressure was used as the best, ethnically acceptable estimate of arterial partial pressure. In particular, the value just before each injection was used because, first, that is the moment when there was a minimum in the rate of uptake and hence in the arterial to end-tidal partial pressure difference.

All anaesthetics were given by one anaesthetist (J. M. C. da S.) in a standard manner, with no supplementary drugs likely to affect MAC or arterial pressure; all ward visits were to be made by that anaesthetist.

If there were any deviations from the study design or any fault in the apparatus or recordings, the results for that patient were excluded from analysis and the name of the corresponding volatile anaesthetic returned to the randomization pool.

MEASUREMENTS AND OBSERVATIONS

For control of depth of anaesthesia

Control of depth of anaesthesia depended primarily on SAP in relation to a “reference” preoperative value. Therefore, first, SAP was measured three times, at intervals, during the preoperative visit and twice in the anaesthesia room. The mean of the two lowest of these five measurements was taken as the “reference” SAP. Second, the same non-invasive arterial pressure monitor (UA731 Auto-inflation-Takeda Medical Inc.) was used on the ward and in the anaesthesia room in all patients; a different monitor (Hewlett Packard No. 78352) was used in theatre on all patients, but the two instruments were used on opposite arms of several patients in the anaesthesia room to check that they gave consistent readings. In theatre, arterial pressure was measured immediately before each injection of liquid anaesthetic and 3 min after those from 4 min onwards.

Both instruments also indicated heart rate which was noted each time arterial pressure was measured. Reference heart rate was taken as the mean of the three ward measurements. Sweating and tears were noted as present or absent just before each injection. Any tears were then dried.

For answering the questions posed

A Normac Anaesthetic Agent Monitor (AA-102 Datex Instrumentarium, Helsinki, Finland) was used for measuring anaesthetic partial pressure throughout anaesthesia. It drew a sample flow of approximately 200 ml min\(^{-1}\) from a side arm on the limb of the closed breathing system. The Normac was calibrated before and after each case, using the calibration canisters supplied by the manufacturer; zero was checked occasionally during each case by briefly sampling room air. End-tidal partial pressure just before each injection of anaesthetic was measured from the chart output, correcting for any slight sensitivity change or zero drift. This gave readings as percentage of ambient atmospheric pressure; therefore barometric pressure was measured to correct to percentage of a standard atmosphere. (This was not done automatically by our Normac.)

Extensive laboratory experiments tested the stability over time of the sensitivity of the measurement system, and the consistency between calibrating mixtures. These showed\(^{10}\) that drift with time was generally within 2% over 1 h, that the pooled SD between different canisters (on any given day) was 1% of the indicated value and that the sensitivities to the contents of the canisters were within 4% of those of gravimetric mixtures of halothane, enflurane or isoflurane in air, made up in the laboratory.

The four stages of recovery of the patient were those used by Saraiva and colleagues\(^{11}\): responds to painful stimulus, obeys commands, answers a simple question, and is fully orientated in time and space. The four questions used on the day after operation were: (a) What is the last thing you remember before going to sleep? (b) What is the first thing you remember after waking up? (c) Did you have any dreams? (If “yes”, what were they?) (d) Would you accept the same type of anaesthetic again?

For supplementary information

A Platon GSYV flowmeter (Platon Flowbits Ltd,
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Hampshire, UK) (50–500 ml min⁻¹) was placed downstream of the Rotameter of the anaesthesia machine to obtain more accurate and precise measurement of oxygen inflow. A Kontron fuel cell measured continuously oxygen concentration in the inspiratory limb of the breathing system. Body temperature was monitored by an oesophageal probe connected to the Hewlett Packard monitor. The readings of these three monitors were noted just before each injection.

Carboxyhaemoglobin concentration was measured (Ciba-Corning Co-oximeter M2500) in blood samples obtained just before induction and just before opening the breathing system for recovery.

For routine clinical monitoring

Arterial saturation was monitored continuously with a pulse oximeter (Novametrix 515); the Hewlett Packard monitor displayed ECG and heart rate. Also, between the latter, widely spaced injections, it automatically measured SAP every 5 min. End-tidal carbon dioxide concentration was monitored by a Datex Normocap instrument, sampling at approximately 100 ml min⁻¹/p57 from the catheter mount for only a few breaths just before each injection, without returning the sample to the breathing system.

PROCEDURE

The circle breathing system

The system had an internal volume of 8 litre. It comprised a jumbo soda-lime canister, 2-litre rubber reservoir bag at the end of 1-m length of rubber corrugated tubing, Y-piece and two 1-m corrugated rubber tubes in each limb. The tube at the anaesthetic-machine end of the expiratory limb had a thickened wall at each end. A 25-gauge needle, mounted on an empty 2-ml glass syringe, penetrated the thickened wall at the machine end. For each injection, the empty syringe was replaced by an appropriately loaded syringe and its contents injected.

No more than two patients were studied on any one day. To reduce cross contamination of anaesthetics, two sets of tubing and reservoir bag were maintained and flushed with oxygen overnight after use. The soda-lime canister was flushed with oxygen 6 litre min⁻¹/p57 overnight before use and the soda-lime was changed before the second patient in one day.

Laboratory experiments¹⁰ showed that with these precautions, cross contamination was always less than 0.05% of an atmosphere.

Apart from the two sets of tubing and bag, the same apparatus was used for all 60 patients with meticulous attention to the sealing of potential leaks and a routine pressure test before each anaesthetic. In the 30 min before induction of anaesthesia, a sequence of operations¹⁰ left the breathing system filled with 55–65% oxygen in nitrogen and ready for an almost loss-free connection to the patient.

Anaesthesia

Patients were premedicated with temazepam 10–30 mg (according to body mass), 1 h before operation. Anaesthesia was induced in the operating theatre with etomidate 0.4 mg kg⁻¹ i.v. One-third of the dose was given first, followed by suxamethonium 1 mg kg⁻¹ i.v. The patient’s lungs were ventilated manually by mask for 1 min, using a Bain breathing system with a fresh-gas flow of oxygen 6 litre min⁻¹, the remainder of the etomidate was then given. After a further 15 s the patient’s trachea was intubated with a cuffed tube, the cuff was inflated, breath sounds were checked and the patient was connected to the circle breathing system. Oxygen inflow was set to the estimated metabolic consumption, and the preset 0-min and 1-min doses were injected as described above.

Thereafter, for a “normal” desired depth of anaesthesia, if SAP just before any dose was due was within 20% of the reference SAP, the general rule was that the previous dose of liquid anaesthetic should be repeated; if SAP was more than 20% greater than the reference, a suitably larger dose was given; if more than 20% below, a smaller dose. This rule was ignored if other signs (increasing heart rate, sweating, tears or, very seldom, extrasystoles) suggested that a larger dose was needed. If a dose was due shortly before the anticipated end of surgery, the required depth was recorded as “light” and the dose was omitted or a small dose given. All doses were recorded.

Manual ventilation was used throughout anaesthesia, with neuromuscular block maintained with vecuronium: a dose of 0.1 mg kg⁻¹ i.v. was given as soon as the effects of suxamethonium began to wear off, followed by additional smaller doses as required. In accordance with local routine practice, crystalloid and sometimes colloid solutions were administered generously, but blood was given only when the estimated blood loss exceeded 20% of the estimated blood volume. Oxygen inflow was adjusted to maintain the volume of the reservoir bag.

At the end of surgery, neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 1.2 mg i.v. and oxygen inflow was increased to 6 litre min⁻¹. When breathing was adequate, the patient was taken to the recovery room breathing oxygen-enriched air from a Hudson mask. Recovery was followed by the anaesthetist, noting the times from opening of the breathing system to each of the four defined stages. The patient was then returned to the ward.

Blinding

For each patient, the anaesthetist was provided with one of a set of identical dark bottles, containing the appropriate liquid anaesthetic, and a sealed opaque envelope containing the name of the anaesthetic. Both were marked only with the serial number of the patient. After the Normac analyser had been calibrated, an assistant opened the envelope, depressed the appropriate selector button on the analyser and concealed the face of the analyser and
the chart record from the anaesthetist throughout the case. To avoid identification of the anaesthetic by smell, the anaesthetist put a few drops of peppermint oil on his surgical mask before opening the numbered bottle of anaesthetic. At the end of the anaesthetic, the assistant rolled up the chart record, sealed it for later analysis and selected enflurane on the analyser so that the anaesthetist could perform the final calibration, still blind. The anaesthetist also wrote down his surmise as to which anaesthetic he had been using. Finally, the assistant marked the anaesthetic on the anaesthetic record card.

**DATA PROCESSING AND STATISTICAL ANALYSIS**

As a reference level for measured end-tidal partial pressures of the anaesthetics, MAC (as a percentage of a standard atmosphere) was calculated from:

\[ \text{MAC} = a \times 10^{bx} \]  

where \( x = \text{difference in age in years from 40,} \)  
\( b = -0.00269 \) and \( a = \text{MAC at age 40 (0.75\%, 1.63\%} \) and 1.17\% for halothane, enflurane and isoflurane respectively).\(^{12}\)

As a reference for the actual doses used, the theoretical unit dose, \( D \), for 1.3 MAC was calculated from:\(^{2}\)

\[ \lambda \) )2 /1 00 /=1.3 \( \times \text{MAC } \times \frac{Q}{r} \]  

where \( \lambda = \text{blood–gas partition coefficient (2.4, 1.9, 1.4 respectively)}^{13} \); \( Q = \text{cardiac output in litre min}^{-1} \), estimated from \( 0.2 \times M^{0.4} \), where \( M = \text{body mass in kg} \) and \( r = \text{ratio of vapour volume at 37°C to liquid volume (240, 210, 206 respectively)}^{5} \). This leads to unit doses of 0.94, 1.86 and 1.00 ml for a 70-kg patient aged 40 yr. Strictly, the dose at 0 min, the “priming” dose, should be calculated differently,\(^{2}\) but the result is usually very similar so the distinction was ignored as is customary among practitioners of the method.

Comparisons between the three agents were generally by one-way analysis of variance (ANOVA), preceded by a log transform for some variables to make the distribution more nearly normal. Where the ANOVA showed a significant difference between anaesthetic agents, comments on individual agents are generally made only when the 95\% confidence intervals of an estimate exclude some expected value. For the irredeemably non-normally distributed volumes of infusion fluid, the Kruskal–Wallis test was used. The chi-square test was used for counts.

Where required, trends of measurements with time were assessed as recommended by Matthews and colleagues\(^{14}\): first a straight line or a parabola was fitted to the results for each patient, then simple statistics were performed on the resulting sets of coefficients (intercept, slope, and curvature), weighting each coefficient in inverse proportion to its variance, as provided by the GLIM package\(^{15}16\) used for the trend analysis and ANOVA.

**Results**

Ninety patients were studied because the results from 30 were discarded for a total of 33 reasons: deviations from study design (eight), faults in the recordings (14), leaks from the breathing system (five) and duration of anaesthesia less than 75 min (six).

**Table 1**  
Patient data. \( s = \text{Superficial, u = upper abdominal, l = lower abdominal} \)

<table>
<thead>
<tr>
<th></th>
<th>Sex (M/F)</th>
<th>ASA grade (I/II)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>Surgery (s/u/l)</th>
<th>Duration of anaesthesia (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Halothane</strong></td>
<td>6/14</td>
<td>13/7</td>
<td>43.6</td>
<td>69.9</td>
<td>1.65</td>
<td>10/4/6</td>
<td>137.4</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>21–65</td>
<td>43–95</td>
<td>1.51–1.85</td>
<td>79–258</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Enflurane</strong></td>
<td>6/14</td>
<td>11/9</td>
<td>45.4</td>
<td>68.0</td>
<td>1.63</td>
<td>67/77</td>
<td>169.1</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>25–63</td>
<td>50–104</td>
<td>1.43–1.85</td>
<td>79–306</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Isoflurane</strong></td>
<td>10/10</td>
<td>13/7</td>
<td>45.4</td>
<td>63.5</td>
<td>1.66</td>
<td>5/9/6</td>
<td>130.3</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>20–65</td>
<td>48–82</td>
<td>1.50–1.80</td>
<td>76–210</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1**  
Mean and 95\% confidence intervals of systolic arterial pressure (SAP) before each injection (as a difference from the reference SAP), against the square root of time, for the three anaesthetics. The positive drift from 9 min onwards is adequately described by a common slope of 1.9 (SEM 0.28) mm Hg per dose interval \( (P<0.001) \). At the later times the means become erratic and the confidence limits wider because the number of patients still anesthetized becomes progressively fewer. Data for enflurane (●) and isoflurane (❖) have been slightly time-shifted relative to halothane (■) to clarify the display.
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The three groups of patients were similar in most respects but mean duration of anaesthesia was greater in the enflurane group (table 1).

PREOPERATIVE RESULTS

The doses of etomidate and suxamethonium were fixed on a mg kg

−1 basis. For the other preoperative variables, the ranges of mean values for the three groups of patients were: temazepam dose 0.323–

0.325 mg kg

−1, reference SAP 127–128 mm Hg and reference heart rate 79–82 beat min

−1.

PEROPERATIVE RESULTS

Haemodynamic variables

SAP increased sharply initially but from 9 min onwards it was, on average, close to the reference SAP for all three anaesthetic agents with a slow but significant (P<0.001) positive drift of 1.7 mm Hg per dose interval, from a little less than the reference SAP to a little more (fig. 1). From 9 min onwards, 86% of individual measurements were within 20% of the reference SAP. This was true both immediately before, and 3 min after, each injection, with a mean decrease of 3–4 mm Hg in that 3 min. Differences between agents were small (<1 mm Hg) and non-significant.

Mean heart rate (before injection) from 9 min onwards was significantly greater than the reference heart rate for enflurane and isoflurane (by 11 and 17 beat min

−1, respectively). With each injection there was a mean decrease of 4 beat min

−1 with halothane.

Clinical signs

Sweating was never observed during the study; tears were recorded only at 1 or 4 min, for six, nine and four patients in the halothane, enflurane and isoflurane groups, respectively. The differences were not significant.

Anaesthetic variables

Mean volumes of liquid anaesthetic injected showed some systematic variation with time (fig. 2) but were similar for all three agents despite the differences in predicted unit dose. Therefore, for each patient, the following values were calculated: predicted dose, mean actual dose (omitting the last one if the required depth at that time was recorded as “light”) and the ratio of the two. These were then averaged for each agent. This showed (upper part of table 2) that the mean enflurane dose was 25% less than that predicted and the mean halothane and isoflurane doses were 24% and 33% more, respectively (P<0.001).

Cardiovascular complications (SAP less than 60% of the reference value, heart rate less than 50 beat min

−1 or greater than 120 beat min

−1, AV junctional rhythm or arrhythmia, or a combination of these) occurred at some time during anaesthesia in 14 patients with halothane, four with enflurane and eight with isoflurane—an overall incidence of 43%. The differences were significant (P<0.01).

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>95%CI</th>
<th>P</th>
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<tbody>
<tr>
<td>Actual volume (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>1.144</td>
<td>0.354</td>
<td>0.98–1.31</td>
<td>ns</td>
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<tr>
<td>Enflurane</td>
<td>1.316</td>
<td>0.399</td>
<td>1.13–1.50</td>
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<tr>
<td>Isoflurane</td>
<td>1.176</td>
<td>0.280</td>
<td>1.04–1.31</td>
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<tr>
<td>Predicted volumea (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>0.921</td>
<td>0.174</td>
<td>0.84–1.00</td>
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<tr>
<td>Enflurane</td>
<td>1.761</td>
<td>0.369</td>
<td>1.59–1.93</td>
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<tr>
<td>Isoflurane</td>
<td>0.901</td>
<td>0.124</td>
<td>0.85–0.96</td>
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<tr>
<td>Ratio (actual/predicted)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>1.237</td>
<td>0.293</td>
<td>1.10–1.37</td>
<td>&lt;0.001</td>
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<tr>
<td>Enflurane</td>
<td>0.752</td>
<td>0.184</td>
<td>0.67–0.84</td>
<td>&lt;0.001</td>
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<tr>
<td>Isoflurane</td>
<td>1.327</td>
<td>0.366</td>
<td>1.16–1.50</td>
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<tr>
<td>Revised predictedb volume (ml)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>0.743</td>
<td>0.354</td>
<td>0.58–0.91</td>
<td>0.03</td>
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<tr>
<td>Enflurane</td>
<td>0.586</td>
<td>0.158</td>
<td>0.51–0.66</td>
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<tr>
<td>Isoflurane</td>
<td>0.550</td>
<td>0.157</td>
<td>0.48–0.62</td>
<td></td>
</tr>
<tr>
<td>Ratio (actual/revised-predicted)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>1.709</td>
<td>0.547</td>
<td>1.45–1.96</td>
<td>0.001</td>
</tr>
<tr>
<td>Enflurane</td>
<td>2.315</td>
<td>0.638</td>
<td>2.02–2.61</td>
<td></td>
</tr>
<tr>
<td>Isoflurane</td>
<td>2.190</td>
<td>0.353</td>
<td>2.03–2.36</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 Mean and 95% confidence intervals of the volumes of injected liquid anaesthetic, against the square root of time, for the three anaesthetics. The final volume was omitted from the calculations when the required depth of anaesthesia at that time was recorded as “light”. The positive drift from 9 min onwards is adequately described by a common slope of 0.066 (95% CI 0.003–0.073) ml per dose interval (P<0.001). Data for enflurane (●) and isoflurane ( ○) have been slightly time-shifted relative to halothane (△) to clarify the display.
partly because some of those patients who underwent prolonged anaesthesia with halothane had consistently large values of $P_e^{\text{bi}}$ throughout anaesthesia.

Steady-state partial pressures were summarized by averaging, for each patient, all $P_e^{\text{bi}}$ values from 49 min onwards, calculating means of these averages for each anaesthetic and also expressing them in MAC units, corrected for age (table 3). The differences between anaesthetics in terms of actual partial pressure were small but, in terms of MAC units, the differences were large (approximately 1, 0.5 and 0.75 MAC for halothane, enflurane and isoflurane, respectively) and highly significant ($P<0.001$).

**Other variables**

Mean rates of vecuronium use were 1.4–1.5 μg kg$^{-1}$ min$^{-1}$ for the three groups. Hartmann’s solution was used in all patients, colloids in approximately 50% and packed red cells in less than 25%. Mean total fluid use ranged from 13 ml kg$^{-1}$ h$^{-1}$ for isoflurane to 16 ml kg$^{-1}$ h$^{-1}$ for halothane. There were no significant differences between anaesthetics in any of these features.

From 9 min onwards overall mean oxygen inflow required to maintain the volume of the breathing system was 212 ml min$^{-1}$ (STPD) with negligible drift and no significant differences between anaesthetics. Allowing for an estimated oxygen leakage of 36 ml min$^{-1}$ (see discussion below) this gives an oxygen consumption of 176 ml min$^{-1}$, close to the 179 ml min$^{-1}$ predicted by Nunn$^{17}$ for our average patient (table 1).

Inspired oxygen concentration was similar for the three agents and averaged 58% overall with all instantaneous values between 42% and 88%.

Overall mean end-tidal $P_{CO_2}$ was 5.0 kPa and overall mean arterial saturation by pulse oximetry was 99%; there were very small differences (<1%) between groups. The lowest recorded saturation was 95%. All but three individual values of end-tidal $P_{CO_2}$ were between 4.0 and 5.9 kPa.

Oesophageal temperature decreased from an overall mean of 36.3°C to 35.8°C at 64 min.

Overall mean carboxyhaemoglobin concentration changed from 2.8% before operation to 3.0% at the end of anaesthesia, with 95% confidence limits for the mean change of $-0.1$ to $+0.4\%$.  

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**Table 3** Geometric mean pre-injection end-tidal partial pressures of anaesthetics (averaged from 49 min onwards). Calculated as follows: (a) logs of all measurements; (b) for each patient, mean of all logs; (c) for each anaesthetic, mean and SD of these log means, that is variation between patients, and 95% confidence interval (CI) of the resulting mean for each anaesthetic; and (d) convert means and CI (but not SD) back to linear values.

*Corrected for age according to equation (1)

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>Geometric mean</th>
<th>sd of logs</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-injection end-tidal partial pressure (% std atmosphere)</td>
<td>Halothane</td>
<td>0.709</td>
<td>0.182</td>
<td>0.58–0.86</td>
</tr>
<tr>
<td></td>
<td>Enflurane</td>
<td>0.670</td>
<td>0.118</td>
<td>0.59–0.76</td>
</tr>
<tr>
<td></td>
<td>Isoflurane</td>
<td>0.870</td>
<td>0.141</td>
<td>0.75–1.01</td>
</tr>
<tr>
<td>Pre-injected end-tidal partial pressure (MAC* units)</td>
<td>Halothane</td>
<td>0.967</td>
<td>0.168</td>
<td>0.81–1.16</td>
</tr>
<tr>
<td></td>
<td>Enflurane</td>
<td>0.425</td>
<td>0.109</td>
<td>0.38–0.48</td>
</tr>
<tr>
<td></td>
<td>Isoflurane</td>
<td>0.769</td>
<td>0.137</td>
<td>0.66–0.89</td>
</tr>
</tbody>
</table>

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**Figure 3** Sample recording of anaesthetic concentration against time. The background grid has been suppressed; a calibration scale (% atmosphere enflurane in this example) and a zero line have been added. Arrows indicate the time in minutes at which each injection was due. Note the sawtooth pattern in inspired (upper limit of trace) and end-tidal (lower limit) concentrations produced by periodic injections of liquid anaesthetic at the times indicated. Note also the occasional zero checks and that no injection was made at 121 min.

**Figure 4** Mean and 95% confidence intervals of pre-injection end-tidal partial pressure ($P_e^{\text{bi}}$) against the square root of time, for the three anaesthetics. The apparent positive drift for halothane after 49 min was not significant ($P=0.5$) and arose partly because some of those patients who underwent prolonged halothane anaesthesia had consistently large values of $P_e^{\text{bi}}$ throughout anaesthesia. Data for enflurane (●) and isoflurane (○) have been slightly time-shifted relative to halothane (□) to clarify the display.
The anaesthetist was generally able to identify the use of halothane, but scored only in accordance with chance in correctly identifying enflurane and isoflurane (table 6).

### Discussion

#### The four questions

- **Are the doses and end-tidal partial pressures consistent with Lowe’s theory?**

The theory is that, if the predicted dose is given at the specified times, arterial partial pressure increases rapidly to the specified level and then remains constant, but there needs to be “procedural modifications according to patient response”.2 In this study the specified level was 1.3 MAC, the doses were given at the specified times, but the sizes of the doses, after the first two, were chosen primarily on the basis of maintaining normal SAP.

- **Anomalies of dosage.** Although all mean actual doses for each anaesthetic were within 33% of predicted (upper part of table 2), steady state values (49 min onwards) of $P_{ET}$ were much less than 1.3 MAC (table 3). Accordingly, the predicted doses for these actual $P_{ET}$ were much smaller and the actual doses were about twice these revised predicted doses (lower part of table 2).

This excess of actual dosage over predicted dosage corresponded to an average excess rate of usage of anaesthetic of approximately 11 ml of vapour per minute. An alternative estimate of excess usage of anaesthetic was obtained from the positive drift of dosage with time (fig. 2) which corresponded to a steady loss of 7 ml of vapour per min.

Several factors could contribute to the apparent need for this excess of 7–11 ml of vapour per min: diffusion into and through the walls of the breathing system; loss in gas leaking from the system; direct uptake into fat from adjacent tissues;18; metabolism, particularly of halothane19; and the fact that, during the period of interest (9–121 min), the theoretical rate of uptake declines a little more slowly than in accordance with the square root of time. Quantitative estimates of these factors (based on laboratory experiments for absorption into the walls of the breathing system) were sufficient to account for a total of 9 ml of vapour per min. Although loss through the skin would be negligible,20 there may have been appreciable loss through the operation wound, especially in those patients undergoing abdominal surgery.21 Similar excesses of uptake over that predicted from the square-root-of-time theory have been reported by others for continuous-inflow versions of the Lowe method.22

- **Anomalies of end-tidal partial pressure.** The clinical aim was to maintain SAP close to the reference level. Therefore, it is not surprising that $P_{ET}$ showed an initial “overpressure” before reaching a steady level (fig. 4). However, as SAP returned to the reference level within 9 min (fig. 1), it is at first surprising that the $P_{ET}$ overpressure lasted until 49 min (fig. 4). However, close inspection of figure 1 reveals that, after the initial hypertension, SAP showed a through at 9–16 min and then drifted back up above the reference level. As SAP was in part inversely dependent on end-tidal partial pressure, this upward drift in SAP can explain some of the decline in $P_{ET}$.
Can the findings of Couto da Silva\textsuperscript{5–8} be replicated in a double-blind study?

The findings that the doses of enflurane required were less than predicted, and that recovery from enflurane was more rapid than that from halothane or isoflurane were confirmed (tables 2, 4) and the study was mostly blind: although the anaesthetist usually identified halothane (table 6), it generally took approximately 25 min to form a firm opinion so that the first five or six injections of halothane (half the average total number) were made blind, as were all injections of enflurane and isoflurane.

Can the cause of the discrepancy between agents be elucidated?

Compared with halothane and isoflurane, enflurane required approximately 50% of the dose (as a fraction of predicted) (upper part of table 2), and produced approximately half the steady-state $P_E'_{bi}$ (in MAC units) (table 3). Therefore, either the MAC of enflurane is less than previously believed or patients who received enflurane were more lightly anaesthetized.

The time taken to reach each of the four stages of recovery was only approximately 50% as long with enflurane as with halothane or isoflurane (table 4), and memories of preoperative events were greater with enflurane, although this was not significant (table 5). Therefore, it must be concluded that patients receiving enflurane were less deeply anaesthetized.

The overall incidence of cardiac rhythm disturbances (43%) was less than the “60% or more” quoted by Atlee\textsuperscript{28} as common, although marginally greater (70%) with halothane. However, these disturbances generally appeared as a new dose became due (and partial pressure was at a minimum) and disappeared soon afterwards.

Mean steady-state $P_E'_{bi}$ was less than the MAC for all three anaesthetics (table 3) (less than 50% of the MAC for enflurane) and the four stages of recovery were reached in times that were very short (table 4) compared with those reported for recovery to the same four stages from halothane and nitrous oxide anaesthesia.\textsuperscript{11} However, no patient admitted to any dreams and all were prepared to have the same type of anaesthetic again. We conclude that anaesthesia was indeed satisfactory although we suggest some improvements below.

LIMITATIONS OF THE PRESENT STUDY

Errors in the measurement of anaesthetic partial pressure

Lowe’s theory is based on arterial partial pressures; we measured end-tidal partial pressures. The former must have been less than the latter throughout our study because of continuing uptake: even just before the last dose, inspired partial pressure was always of negligible importance. As methane is produced by microbial fermentation of carbohydrates, mainly in the distal colon,\textsuperscript{30} the difference from patients in Belgium may perhaps be related to a difference in gut flora or diet.

Differences between end-tidal and arterial partial pressure

Lowe’s theory is based on arterial partial pressures; we measured end-tidal partial pressures. The former must have been less than the latter throughout our study because of continuing uptake: even just before the last dose, inspired partial pressure was always a little greater than end-tidal. However, virtually all MAC values are based\textsuperscript{29} on measurements of end-tidal partial pressure. Therefore, our $P_E'_{bi}$ values expressed in MAC units should be consistent with those in other studies.

Leakage rate

The outflow from the Normac analyser includes a small flow of air (30 ml min$^{-1}$ in our analyser) drawn in as a reference gas. The nitrogen content of this air (24 ml min$^{-1}$) forms a convenient tracer gas from which leakage can be calculated. First, after approximately 2 h, oxygen concentration in the breathing system reached a plateau (60% on average). Therefore, at that time, the inflow of nitrogen must have equalled the outflow, and nitrogen excretion from the body would by then be negligible. Accordingly, the 24 ml min$^{-1}$ from the Normac formed 40% of the leakage rate. Therefore, total leakage was approximately 60 ml min$^{-1}$ and included approximately 36 ml min$^{-1}$ of oxygen.

LIMITATIONS AND IMPROVEMENTS OF THIS METHOD OF ANAESTHESIA

Although 30 of 90 patients were excluded, in only six
instances were the causes relevant to clinical use of the technique: five of these were leaks (only one of which led to abandonment of the closed system) and one was use of adrenaline by the surgeon which interfered with judgement of depth of anaesthesia. Therefore, the technique is widely applicable.

The instance of adrenaline use draws attention to a general problem in using arterial pressure as a main measure of depth of anaesthesia: any drug, or other event, that has a direct effect on arterial pressure but not on depth of anaesthesia must be avoided, or allowed for, or another method of assessing depth must be used.

In routine clinical practice, anaesthesia could be deepened rapidly or lightened at any time by an extra injection or by opening the system, or even by inserting a charcoal absorber. However, the need did not arise in any of the 90 patients entered into this study.

We used a short-acting non-analgesic induction agent (etomidate) and no opioid, to ensure minimum interference with comparison of the volatile agents. Therefore, in routine clinical practice, the initial hypertension could be reduced by using more appropriate drugs and reducing the early doses of liquid anaesthetic correspondingly.

An enflurane Petbi value of 0.42 MAC obviously raises concerns about awareness, even though MAC-awake (the concentration at which the patient just responds to command) has been reported to be 0.27 MAC for enflurane. In this respect, it is important to note that the zero incidence of awareness found in our 20 patients implies that the upper 95% confidence limit, for the incidence in a population, in our 20 patients implies that the upper 95% confidence limit, for the incidence in a population, in our 20 patients implies that the upper 95%

References


