Model-based administration of inhalation anaesthesia.

4. Applying the system model

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Background. We developed and tested a simple dosing strategy for rapid induction with isoflurane followed by maintenance under minimal-flow conditions, that is 0.5 litre min⁻¹ total fresh gas flow (FGF). An end-expired concentration was to be achieved within 5 min in a desired therapeutic window, that is 0.8–1.1 vol%, and to be maintained within it for at least 30 min.

Methods. With our new model we computed a three-stage regimen using one fixed vaporizer setting: 3 vol% isoflurane in a FGF of 3 and 1.5 litre min⁻¹, each for 3 min, and 0.5 litre min⁻¹ thereafter. The ratio of nitrous oxide:oxygen was, consecutively, 2:1, 2:1, and 2:3. We evaluated this scheme in 58 adult patients (body mass 74 (SD 13) kg), mostly during eye and ear, nose, and throat surgery.

Results. Measured oxygen (33–45 vol%) and nitrous oxide concentrations (66–50 vol%) evolved in accordance with those computed. In five patients with a median of body mass 92 kg (range 76–126 kg), inspired oxygen concentrations decreased to less than 30 vol%. End-expired isoflurane concentration entered the window after 2 min (range 1.0–5.67 min) and attained its maximum, that is 0.96 vol% (0.8–1.2 vol%), after 3.45 min (1.67–6.33 min). The mean end-expired concentration was in the desired window from 3–60 min and an average of 72% of individual measurements were within the window from 3–30 min. The scheme was adapted in six patients (excluded from analysis) because of hypotension.

Conclusion. The regimen is easily remembered, reliable, and lends itself to alternative strategies, but must be guided by the monitoring of gas and vapour concentrations and haemodynamic variables.

Br J Anaesth 2002; 88: 175–83

Keywords: anaesthetics volatile, isoflurane; pharmacokinetics, models; anaesthetic techniques, inhalation; equipment, breathing systems

Accepted for publication: September 9, 2001

The technique of low-flow anaesthesia (≤1 litre min⁻¹ total fresh gas flow (FGF)) is a dichotomy. On the one hand, this technique offers many advantages; on the other, it is poorly accepted. For example, it is recognized that it is very economical and reduces environmental pollution. Technical barriers no longer exist as modern anaesthesia systems integrate all the necessary equipment to facilitate safe administration. Nevertheless, low-flow techniques are still not universally used in current clinical practice. A major problem is the lack of a simple dosing strategy that aids in attaining and maintaining pre-defined concentrations of the inhaled anaesthetics.

Our principal aim was to develop such a dosing strategy capable of achieving low-flow conditions in a few minutes and able to work within the time constraints of a routine session. Thus, the desired concentration of an inhaled anaesthetic had to be attained rapidly, as anaesthesia should be adequate early in the operation, and with a minimum of manual interventions. Also, the dosing regimen had to be simple enough to be easily remembered and easily applied without any calculations.
Devising a suitable regimen in the clinical environment might prove to be difficult or even dangerous to patients. Therefore, we applied version 2 of our system model, recently developed and validated for desflurane.1±3 We now present: (i) the theoretical testing of potentially useful dosing strategies through different ‘what happens if’ scenarios; (ii) the clinical validation of a mnemonic (easily remembered) sequence of vaporizer settings and flows for isoflurane in a mixture of nitrous oxide and oxygen.

**Patients and methods**

The study proceeded in two steps: a computer study was followed by clinical testing.

**Computer study**

The dosing strategies tested were based on our practical experience with various low-flow techniques. Minimum requirements were that the end-expired isoflurane concentration would: (i) enter a therapeutic window of 0.8–1.1 vol% within 5 min; (ii) remain within that window for at least 30 min under low-flow (total FGF ≤ 1 litre min⁻¹) and preferably ‘minimal-flow’ conditions (total FGF=0.5 litre min⁻¹).

Of all schemes tested, only three (A–C) will be illustrated. They have to be judged against the minimum requirements as well as additional practical and theoretical arguments. These schemes and the pre-scheme gas flows are given in Table 1. Zero time is the start of the administration of isoflurane.

Scheme A is a four-stage scheme using the maximum vaporizer setting to hasten induction with a FGF of 1 litre min⁻¹. Only the vaporizer setting is adjusted during the course of the anaesthetic.

**Table 1** Sequences of FGF and vaporizer settings in the three isoflurane dosing schemes (A–C) tested by computer simulation. The pre-scheme gas flows were 9–12 litre min⁻¹ air (3 min), 5 litre min⁻¹ each of nitrous oxide and oxygen (2 min), and 6 litre min⁻¹ nitrous oxide in 3 litre min⁻¹ oxygen (5 min).

<table>
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<th>Stage</th>
<th>Time (min)</th>
<th>FGF oxygen (litre min⁻¹)</th>
<th>FGF nitrous oxide (litre min⁻¹)</th>
<th>Vaporizer setting (vol%)</th>
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<tr>
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<td>0.5</td>
<td>1</td>
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<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>0.3</td>
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</table>

Simulation with scheme C were performed for three typical patients of different body sizes and age (Table 2), aiming at an ‘ideal’ alveolar carbon dioxide tension of 5.33 kPa. End-expired concentrations of gas species were calculated as described elsewhere. Nitrous oxide concentrations were averaged over the respiratory cycle (=the sum of one-third of the inspired and two-thirds of the end-expired concentration (I:E ratio=1:2)) to match measured nitrous oxide concentrations (vide infra).

<table>
<thead>
<tr>
<th></th>
<th>S</th>
<th>M</th>
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<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
</tr>
</tbody>
</table>

Scheme B, being a variant of A, eventually uses minimal-flow conditions and therefore necessarily uses 2.5 vol% isoflurane and not 2 vol% as A. In scheme B both the vaporizer and Rotameter settings must be adjusted.

Scheme C is a three-stage scheme starting with a relatively high flow of fresh gas for a very short period. The vaporizer setting remains the same throughout the anaesthetic. Only the FGF is adjusted. The scheme starts with three times the number ‘three’: 3 vol% isoflurane in 3 litre min⁻¹ fresh gas for 3 min. After the first 3 min the FGF is halved. After another 3-min period, the FGF is reduced to the preferred minimal-flow conditions. All three schemes satisfied our minimum requirements (i) and (ii) above), but scheme C was selected for clinical testing because it appeared to be simple as well as mnemonic.

Simulations with scheme C were performed for three typical patients of different body sizes and age (Table 2), aiming at an ‘ideal’ alveolar carbon dioxide tension of 5.33 kPa. End-expired concentrations of gas species were calculated as described elsewhere. Nitrous oxide concentrations were averaged over the respiratory cycle (=the sum of one-third of the inspired and two-thirds of the end-expired concentration (I:E ratio=1:2)) to match measured nitrous oxide concentrations (vide infra).

**Clinical study**

**Anaesthetic management**

Seventy-eight consenting patients (ASA Physical Status I–II; age 17–69 yr) were studied after approval of the Institutional Ethics and Research Committee. They were to undergo elective surgical procedures expected to last at least 45 min and to cause negligible blood loss (eye or maxillofacial surgery, mostly ear, nose, and throat (ENT), and one patient for lumbar laminectomy). Oxazepam 10–30 mg was given orally 1 h before surgery. An intravenous (i.v.) catheter was inserted and basic monitoring (ECG, non-invasive arterial pressure (NIBP), heart rate, arterial saturation by pulse oximetry) established. Arterial pressure was measured with a 1-min interval for 60 min, a 3- to 5-min interval thereafter, and whenever judged necessary by the attending anaesthetist (R.V.).
Anaesthesia was induced with fentanyl 0.1–0.2 mg i.v. and a dose of thiopental sufficient to obtund the eyelash reflex, followed by vecuronium or rocuronium. The patient’s lungs were ventilated manually by mask for 2–3 min using a FGF of 10 litre min\(^{-1}\) (nitrous oxide:oxygen, 1:1 ratio). Following tracheal intubation with a cuffed tube, the patient’s lungs were artificially ventilated with a high FGF of 9 litre min\(^{-1}\) (nitrous oxide:oxygen, 2:1) for 5–10 min. Additional doses of i.v. anaesthetic were given as judged appropriate. Prophylactic antiemetic therapy was given at 10 mg or/and droperidol 1.25–2.5 mg i.v. at the discretion of the attending anaesthetist (metoclopramide from a point between the Y-piece and the tracheal tube to redirect the system to the breathing system, as well as the reference room air taken by the analyser to calibrate its zero baseline at preset intervals (three times during the first hour after switching on the anaesthesia system, and every hour thereafter; calibration lasts 15 s).

Following the period with high FGF, scheme C was applied (Table 1). The timer of the anaesthesia system was used to measure the time periods. During maintenance we did not modify the isoflurane administration unless the patient’s responses required so (vide infra). We therefore monitored the response of the patient to surgery by the assessment of NIBP, heart rate, and heart rate variability judged by ear with the aid of pulse oximetry, as well as the end-expired isoflurane concentration. Extra fentanyl (increments of 0.05–0.1 mg) was given intravenously according to clinical needs. The lungs were ventilated with a ventilatory frequency of 10–12 bpm (I:E ratio of 1:2) and a tidal volume sufficient to maintain the end-expired carbon dioxide tension at 3.7–4.7 kPa.

**Equipment**

The anaesthetic equipment consisted of the Modulus CD anaesthesia system (Ohmeda, Madison, USA) as routinely used in our operating theatres for eye, ENT, and neurosurgery. An ARKIVE automated anaesthesia record-keeper provided a computerized anaesthetic record of patient’s vital signs. All monitored data were saved on a floppy disk drive integrated in the anaesthesia system.

The anaesthetic breathing system comprised a soda-lime canister (part of the Ohmeda GMS (Gas Management System) Absorber), two 1-m corrugated tubes in each limb, a water trap in each limb, and a Y-piece. A switch in the GMS allows swift alternation between reservoir bag and ventilator. A 2-litre bag at the end of 1-m length of corrugated tubing was used for spontaneous breathing and manual ventilation by mask. A standing bellows ventilator (Ohmeda 7850) supported artificial ventilation of the lungs. A scheme of the breathing system with an internal volume of 6.6 litre, as used during artificial ventilation, is given elsewhere.\(^1\) Leaks in the circuit were detected by plugging the Y-piece, pressurizing the breathing system to 4 kPa, and observing the volume and pressure gauge; a gas leak up to 60 ml min\(^{-1}\) was accepted.

The integrated infrared multi gas monitor sampled gas from a point between the Y-piece and the tracheal tube to assess inspired and end-expired carbon dioxide and isoflurane concentrations, as well as nitrous oxide concentrations averaged over the whole respiratory cycle. The analyser was calibrated once per day with room air and a canister of gas provided by the manufacturer. We verified the calibration for isoflurane with a calibration gas mixture containing 1 vol% isoflurane in 30 vol% oxygen, 30 vol% nitrous oxide, and balance gas nitrogen (AGA Gas, The Netherlands). Sample gases (150–230 ml min\(^{-1}\)) were redirected to the breathing system, as well as the reference room air taken by the analyser to calibrate its zero baseline at preset intervals (three times during the first hour after switching on the anaesthesia system, and every hour thereafter; calibration lasts 15 s).

Oxygen was measured with the integrated fuel cell, calibrated with room air. The accuracy of the Rotameters was checked against a bubble flow meter. Isoflurane was delivered to all patients by the same Ohmeda Tec 5 vaporizer.

**Data handling**

From the variables saved on floppy disk the following were analysed: inspiratory oxygen and averaged nitrous oxide concentrations (rounded to whole percentages), inspiratory and end-expired isoflurane concentrations (rounded to one decimal), heart rate, and NIBP (systolic (SAP) and diastolic (DAP) arterial pressure). Basically, gas and vapour concentrations were studied at 20 s, heart rate and NIBP at 1-min intervals. This basic scheme could not be applied throughout because the study data were saved in two different ways, as a result of an unavoidable upgrading of the system software in the course of the study.

The old software saved all variables, except NIBP, at 20-s intervals, for example at 0, 20, 40, 60, 80, 100 s, etc. After each measurement of the NIBP, all variables, including NIBP, were saved in addition to the basic 20-s scheme. Thus, no values were available at the 20-s interval nearest the time point where NIBP was saved. In our example, no data would be saved at 20 and 80 s. This led to ‘missing values’. The values for the gases and vapours saved along with the NIBP could not be used because rounding off to the nearest time point would have distorted the time course of the gas and vapour concentrations.

**Haemodynamic variables**

To evaluate the haemodynamic effects of using scheme C, we assessed the variation with time of arterial pressure and heart rate. The last values obtained before the administration of isoflurane were judged adequate by the attending anaesthetist (R.V.) and used as reference values. The haemodynamic variables were studied until the isoflurane administration was discontinued.

Bradycardia (heart rate <40 beats min\(^{-1}\) for at least 30 s) caused by the oculocardiac reflex was treated with 0.5 mg atropine i.v. and by releasing traction on extraocular muscles. Hypotension was defined as SAP less than 80.
mm Hg for at least 2 min. For middle ear surgery, parotidectomy, and dacryocystorhinostomy, hypotension was defined as a SAP less than 70 mm Hg for at least 3 min because a reduction in arterial pressure was used to provide good operating conditions. Hypotension was initially treated with i.v. replacement therapy. Hypotension lasting longer than 5 min was treated by reduction of the end-expired isoflurane concentration. The time was noted when this occurred and these patients were excluded from analysis.

**Performance indicators**

To assess the performance of scheme C, we identified the point count (PC). This is the percentage of measured end-expired isoflurane values below, within, and above the therapeutic window of 0.8–1.1 vol% for each 3-min interval of the first 30 min after the introduction of isoflurane. Note that the values 0.8 and 1.1 vol% belong to the window.

PC was calculated for: (i) pooled data from all patients; and (ii) each patient. From the latter PC, we assessed the number of those patients for whom all end-tidal isoflurane concentrations, observed in a 3-min period, were below, within, or above the window, and of those with concentrations crossing the 0.8 or 1.1 vol% limit.

A detailed analysis of the first 7 min of the anaesthetic, that is the initial phase of isoflurane wash-in, was performed to detect: (i) onset time ($t_{\text{onset}}$), that is the time needed to attain the therapeutic window; (ii) $C_{\text{max}}$, that is the maximum end-expired concentration; and (iii) $t_{\text{max}}$, that is the time needed to attain $C_{\text{max}}$.

**Regression analysis**

A regression line of end-expired isoflurane concentrations against time (from 15–60 min) was calculated for: (i) scheme C in patient M; and (ii) each of the patients retained in the clinical study. The individual estimated slopes were averaged over the patients and reported as mean (SD) and 95% confidence interval (CI).

**Results**

**Computer study**

Figure 1 illustrates selected computed results. For three typical patients, the complete time courses of the oxygen and nitrous oxide concentrations only differed slightly across the different schemes (not shown). For the same scheme, however, there are clinically important differences between model patients. This is illustrated for scheme C in Figure 1 (upper). Under low-flow or minimal-flow conditions (6–60 min), the inspiratory concentrations of oxygen evolve approximately between 30 and 45 vol% for the standard patient M, and the averaged concentrations of nitrous oxide between 65 and 55 vol%.

In patient M, schemes A and B cause the end-tidal isoflurane concentration to enter the therapeutic window after 4 min and to stay within the window until 60 min (Fig. 1, lower). As a result of scheme A, the isoflurane concentration stays in the middle half from 4 to 60 min. As a result of C, the isoflurane concentration enters the window after 2 min, stays within it until 60 min, and even travels in the middle half from 2.5 to 60 min, except for the period 9–24 min. The regression line (15–60 min) has an intercept of 0.78 vol% and a positive slope of 0.0042 vol% min$^{-1}$.

In patients S and L, however, scheme C causes the end-expired isoflurane concentration to enter the therapeutic window after 1.5 and 2.5 min, respectively, and results in an overshoot (>40 min) or undershoot (7–40 min), respectively.

The three schemes do not differ grossly as to the product of the duration of administration of isoflurane and the sum of the end-expired concentrations of nitrous oxide and isoflurane, expressed as multiples of MAC: 1.3, 1.22, and 1.3 MAC×hours for schemes A, B, and C (patient M), respectively. The calculated usage of liquid isoflurane for schemes A, B, and C in 60 min is 7.4, 5.7, and 6.2 ml, respectively. The relatively high flow in C needed for rapid induction results in a usage 9% greater than that of B.

**Clinical study**

The results are based on data from 58 patients because the data from 20 were discarded for three reasons: technical failures (eight), duration of isoflurane administration for less than 30 min (six), hypotension (five), and both hypotension and duration for less than 30 min (one). If hypotension occurred, it was always within 30 min of the start of isoflurane administration.

The characteristics of the average patient in the study (Table 3) are in reasonable agreement with those of our model subject (patient M; Table 2). One male patient may be designated an outlier because of his body mass index which was 35.6 kg m$^{-2}$. Recovery from the anaesthetic was uneventful in all patients.

The average measured oxygen and nitrous oxide concentrations (Fig. 2) were in close agreement with those predicted for patient M. Oxygen concentrations slowly increased from approximately 33 to 45 vol%, whereas nitrous oxide concentrations slowly decreased from approximately 66 to 50 vol%. In five patients with 92 kg as median body mass (range 76–126 kg), inspired oxygen concentrations decreased to less than 30 vol%. The number of patients still anaesthetized became progressively fewer after 30 min. Most results from the clinical study were limited to the first 60 min of anaesthesia because after 60 min the number of patients became less than 30 (Fig. 2).

Figure 3 shows that, between the 15 and 60 min, there was a slight positive drift in the inspired concentration of isoflurane from approximately 1.1 to 1.2 vol%. The ratio of inspired concentration to vaporizer setting was approximately 1:3 for 7–60 min. The group slope of the regression lines of end-expired isoflurane against time (15–60 min)—
averaged over 58 patients—was 0.0035 (0.0024) vol% min⁻¹ with a 95% CI from 0.0028 to 0.0041 vol% min⁻¹.

Table 4 shows PCs from pooled data obtained after applying dosing strategy C. Within 6 min, the PC within the window was greater than 90%, then decreased to stabilize at around 66%, and eventually scored 75% at 30 min.

Figures 4–6 focus on the individual curves, especially in the early phases. Scheme C satisfied our requirements for the majority of patients. From 3–30 min, 60–83% of the patients remained fully within the predetermined window (Fig. 4). Almost all patients were crossing the lower limit in the first period (0–3 min), and patients suffering from overshoot were virtually absent (Fig. 4). The average onset time $t_{\text{onset}}$ was approximately 2 min, and for all but three patients $t_{\text{onset}} \leq 3$ min (range 1.0–5.67 min) (Fig. 5). Figure 6 gives the plot of peak isoflurane concentrations against the

| Table 3 Patient data. e=eye, m=maxillofacial (mostly ENT), l=lumbar laminectomy. BMI=body mass index (patients with a BMI <20 kg m⁻² are considered slender; patients with a BMI >25 kg m⁻² are designated obese) |
|---|---|---|---|---|
| Sex (M/F) | ASA grade (I/II) | Age (yr) | Body mass (kg) | Height (m) | BMI (kg m⁻²) | Surgery (e/m/l) |
| N 34/24 | 33/25 | Mean (SD) | 42 (16) | 74 (13) | 1.73 (0.11) | 24.95 (3.07) |
| Mean (SD) | 17–69 | 54–126 | 1.52–1.96 | 18–35.6 |
| Range | | | | | | |

Inhalation anaesthesia model: clinical application

Fig 1 Selected simulations resulting from schemes A, B, or C (Table 1) for three typical patients of different body size and age (Table 2). (Upper) Inspired oxygen and averaged nitrous oxide concentrations plotted against time, as a result of applying scheme C, for a small (S), medium (M), or large (L) patient. (Lower) End-expired isoflurane concentrations resulting from schemes A and B for a medium patient, and from scheme C for a small, medium, and large patient. Time 0=time point at which isoflurane is introduced. The shaded areas mark the therapeutic window (0.8–1.1 vol%; grey) and its middle half (0.875–1.025 vol%; light grey). The aim was that end-expired isoflurane concentrations would enter the desired window in less than 5 min and would stay within that window for at least 30 min. The vertical lines mark 5 and 35 min after the start of isoflurane administration.
time the maximum occurs. The maximum concentration was attained within 3 min in 38, and within 6 min in 56 out of 58 patients. $t_{\text{max}}$ averaged 3.45 min (range 1.67–6.33 min), whereas $C_{\text{max}}$ averaged 0.96 vol% (range 0.8–1.2 vol%). Observations that fell outside the therapeutic window were mostly ‘too low’—with isoflurane concentrations always $>0.6$ vol% (Fig. 4).

Figure 7 illustrates the haemodynamic variables against time. Reference values (mean (SD)) for SAP, DAP, and heart rate were 121 (25) mm Hg, 72 (14) mm Hg, and 75 (14) beats min$^{-1}$, respectively. Initially SAP and DAP decreased sharply to 109 (19) and 63 (11) mm Hg, respectively, and from 6 min onwards they showed a slow negative drift of 0.18 ($P<0.001$) and 0.11 mm Hg min$^{-1}$ ($P<0.001$), respectively. Atropine was given to 14 patients.

Discussion
The main objective of the present study was to develop and to test a dosing strategy for the rapid induction of a low-flow isoflurane anaesthetic in order to improve clinical conditions during the first 30 min of anaesthesia. Although there are proposals in the literature for the maintenance of anaesthesia, there is only one report describing strategies to rapidly achieve and maintain a predetermined level of anaesthetic under low-flow conditions. No experimental validation was performed, however, and only the administration of inhalation anaesthetics in oxygen was studied.
We realized that if the scheme was to have practical value it had to be appealing, attractively simple, easily remembered, and yet effective. As long as the average clinical anaesthetist does not have access to a computer-controlled system and must resort to manual adjustment of the vaporizer and Rotameters, any dosing strategy adds to their array of tasks. Complex dosing schedules derived from a model may, therefore, receive low priority compared with direct patient care. A practical dosing scheme should offer a balance between feasibility, reliability, and the potential for economic savings.

Our criteria were translated into the following specific requirements. The end-expired isoflurane concentration should enter the desired therapeutic window, 0.8–1.1 vol%, in less than 5 min and should stay within that window for at least 30 min under minimal-flow conditions. The total number of adjustments of the vaporizer and Rotameters should be minimal. The time period during which adjustments have to be made should be short. If these requirements are met, the anaesthetist can focus on the patient during a busy anaesthetic and yet rely upon the effectiveness and reliability of the dosing strategy.

Scheme C proved to match our requirements: reliable wash-in was obtained by setting the vaporizer once (the vaporizer is turned to the chosen setting, and is then left unaltered throughout the operation) and the Rotameters three times within a 6-min period. After 3 min the average end-expired concentration was a little over 0.9 vol% (Fig. 3); individual measurements fell outside the pre-defined window but, from 3 min onwards, at least 63% were within the window with almost all the remainder falling below it (Table 4).

In Figure 3 (10–20 min), the mean measured isoflurane concentration is close to 0.8 vol%, which superficially suggests that 50% of individual measurements should be ‘low’, against the 28–38% in Table 4. However, as the infrared analyser reads only to the nearest 0.1 vol%, a

<table>
<thead>
<tr>
<th>Period (min)</th>
<th>‘Too low’ (&lt;0.8 vol%) (%)</th>
<th>Within window (0.8 vol% and ≤1.1 vol%) (%)</th>
<th>‘Too high’ (&gt;1.1 vol%) (%)</th>
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<tr>
<td>0–3</td>
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**Table 4** Performance analysis for scheme C (Table 1) based on PCs from pooled data. There were 461 to 518 measuring points per 3-min period. PCs are percentages of measuring points below, within, and above the therapeutic window, i.e. 0.8–1.1 vol% end-expired isoflurane concentration, for each 3-min period. **Fig 4** Performance of scheme C for the first 30 min. Numbers of patients, expressed as percentages of the total number (n=58), that fall into the following five categories: patients for whom all end-tidal isoflurane concentrations, observed in a 3-min period, were below (‘too low’), within (≥0.8 vol% and ≤1.1 vol%), or above (‘too high’) the therapeutic window, and of those with isoflurane concentrations crossing the 0.8 or 1.1 vol% boundary in the same period of time. The data total 100%. For example, from 12–15 min the isoflurane concentrations were ‘within the therapeutic window’ for 60%, ‘too low’ for 26%, and ‘crossing 0.8 vol%’ for 14% of the patients.

**Fig 5** Detailed analysis of the first 7 min: distribution of individual onset times (t<sub>onset</sub>) for end-tidal isoflurane concentrations, that is the time needed to attain the therapeutic window. Each patient is represented by one symbol (open circle): 95% of the population (55 out of 58 patients) had an onset time ≤3 min. The aim was that end-expired isoflurane concentrations would enter the desired window in less than 5 min.
reading of less than 0.8 vol% really means less than 0.75 vol%. With an SD of approximately 0.1 vol%, this means that only those patients more than 0.5 SD below the mean concentration will be classed as 'too low' which, for a Gaussian distribution, would be 31%, in better agreement with Table 4.

An upward trend in end-expired concentration in the 15–60 min period was found experimentally as well as in the model (Fig. 3). The slope was only 80% that in the model but still suggests that uptake was not constant in that period. This agrees with recent findings, but conflicts with the interpretation of other work.

Fig 6 Detailed analysis of the first 7 min: scatter plot of maximum end-expired isoflurane concentration ($C_{\text{max}}$) by time of maximum ($t_{\text{max}}$). Each patient is represented by one open circle ($n=58$). Circles to be plotted on the same point remain visible by adjusting their radii to the number of observations at the same point.

Fig 7 Haemodynamic variables. The SAP and DAP and the heart rate are shown (left y-axis) along with the number of observations (step plot without symbols; right y-axis). The heavy lines represent means of arterial pressures and heart rate. The spread of data is reflected by 1 SD in the positive (SAP and heart rate) or negative direction (DAP) at −1, 0, 3, 6, and 10 min, and at 10-min intervals thereafter. Time zero is the start of isoflurane administration.
Although scheme C is less economical than B, there is a practical argument (other than rapid induction with isoflurane) to use more than 1 litre min\(^{-1}\) during the early stages of anaesthesia. Nitrous oxide uptake may still be unpredictably high. Using a total FGF of 3 and 1.5 litre min\(^{-1}\), each for 3 min, helps to prevent lack of gas in the circle system. If a shortage of fresh gas should occur, ventilation may be less than optimal, alarms may need to be silenced, and time-consuming adjustments of the Rotameters would be necessary.

There are clinically important arguments against the use of schemes A and B, both using 5 and 4 vol% isoflurane. At such high settings, vaporizer output may deviate more from that set on the dial than at lower settings.\(^8\)\(^9\) Thus, schemes A and B may prove to be less reliable than C. Furthermore, scheme C requires less adjustments than A or B and these occur in a shorter time period (Table 1). Nevertheless, scheme A might be a good choice for those who wish to use a FGF $\geq$1 litre min\(^{-1}\). Obviously, scheme A lacks clinical testing.

We have found that scheme C is appealing and easily remembered. Although it reflects ‘very-nearly-closed-circuit anaesthesia’,\(^10\) it does not have a steep learning curve, and trainees remember the scheme well after using it for only a few anaesthetics. The combination of three times the number three appears to be a key factor. Indeed, the (three-step) scheme starts with 3 vol% isoflurane in a ‘full flow’ of 3 litre min\(^{-1}\) for 3 min. This is followed by a ‘half flow’ of 1.5 litre min\(^{-1}\), again for 3 min, and ‘minimal flow’ of 0.5 litre min\(^{-1}\) thereafter.

Clear caveats have to be made about clinical implementations of theoretical results.\(^5\) Scheme C was never intended to be used as a rigid recipe, but rather as a ‘rule of thumb’ or starting regimen that should be adjusted to the individual needs of the patient.\(^11\) Valuable tools for that purpose are sound clinical judgement and appropriate monitoring of concentrations of anaesthetic as well as haemodynamic variables. Rapid build-up of concentrations of a potent inhalation anaesthetic can have clinically important haemodynamic consequences. Thus, a short interval time for the assessment of NIBP is necessary during the early phases, especially in the absence of surgical stimulation.

Similarly, measurement of the inspired oxygen tension is indispensable when using fixed low flows with nitrous oxide. Under ‘minimal-flow’ conditions, nitrous oxide accumulates in the circuit because nitrous oxide uptake diminishes as time passes.\(^4\) It follows that, oxygen uptake being unchanged, the oxygen tension decreases with time (Fig. 6 in ref. 2). In accordance with the findings\(^4\) of Virtue, 200 ml min\(^{-1}\) of nitrous oxide in 300 ml min\(^{-1}\) of oxygen appears to be the right base for an idealized 70 kg patient (Fig. 2). Nevertheless, inspired oxygen fractions less than 0.3 may develop, especially in patients weighing more than average. This occurred in five patients with a median body mass of 92 kg (range 76–126 kg) for $\geq$5 min in the first 120 min of the anaesthetic, while $pO_2$ was always $\geq$92%. Monitoring must permit early correction of FGF.

Anaesthetists often point out that the main disadvantage of low-flow techniques is that the inspired anaesthetic gas concentration is not directly related to the vaporizer setting. One must realize, however, that the inspired concentration is a clinically less important value than the end-expired concentration, because the effects of inhaled anaesthetics are related to the latter.

Our results suggest that a three-step scheme using 3 vol% isoflurane in a ‘full flow’ of 3 litre min\(^{-1}\) and a ‘half flow’ of 1.5 litre min\(^{-1}\), each for 3 min, with ‘maintenance’ of 0.5 litre min\(^{-1}\) thereafter, is an easily remembered dosing strategy maintaining an end-expired concentration of approximately 1 vol% for 60 min. As a rapid induction with a potent volatile anaesthetic agent is obtained, close monitoring of vapour concentrations and haemodynamic variables is mandatory.

Acknowledgement
We thank M.C.J. De Ruiter, BSc, for excellent data management.

References
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