We compared the time to reach two anaesthetic end-points during induction of anaesthesia with a potent inhalation agent (sevoflurane) and an i.v. agent (propofol). We used a method to ensure steady breathing during inhalation induction, and measured loss of tone in the outstretched arm and loss of response to a painful stimulus. Thirty-eight female patients (age 39 (9) yr, weight 65 (11) kg, and height 165 (8) cm (mean (SD)) were randomly allocated to receive either propofol or sevoflurane. The predicted induction dose of propofol, estimated from age and weight for each patient, was given at a rate of 1% of the induction dose per second, to a possible maximum of 2.5 times the predicted induction dose. Sevoflurane was given with an inhaled concentration of 8%, which was anticipated to cause loss of arm tone within 90–120 s. After loss of consciousness, we applied a painful electrical stimulus to a finger at 15-s intervals and measured the time to loss of motor response. The median times and interquartile values for loss of arm tone were 105 (88–121) s for sevoflurane and 65 (58–80) s for propofol. This was equivalent to 0.65 of the ED$_{50}$ of propofol. The time to loss of response to pain was 226 (169–300) s for sevoflurane. The variances of these three measurements were not significantly different, indicating that these dose–response relationships were similar. In contrast, only 11 of the patients given propofol lost the response to pain after 2.5×ED$_{50}$ had been given. These results support previous evidence of substantial differences between anaesthetic end-points, and show that this evidence can be obtained using a simple and rapid method.
Clinical investigations of induction of anaesthesia use a variety of measures of anaesthetic effect. Anaesthetics probably do not have a ‘single’ effect: two obvious separate effects that have been studied are obtunding (loss of volition), and immobilizing (loss of motor response to pain). For some anaesthetics, such as the potent inhalation agents, these effects may be proportional, and have similar dose–response curves. For other types of anaesthetics, such as the i.v. agents, there may be marked differences in the pattern of these effects.

A full examination of the relationship between different measures of anaesthetic action needs stable drug effects obtained in prolonged studies using infusions. If the main interest is the relative distribution of these end-points, for example when comparing agents whose actions are suspected to have different mechanisms, then it is possible to study subjects as the drug effect progressively increases. We have found that the time to loss of reflex caused by propofol is more variable than other measures such as loss of voluntary control of breathing and motor activity. We were able to study steadily increasing depth of sevoflurane anaesthesia by using a method which allows breathing to continue without interruption during induction of anaesthesia.

Propofol and sevoflurane are two agents often used to induce anaesthesia for day case surgery. We compared these two different induction agents because they have different patterns of action, comparing a response that is typical of ‘obtundling’ (loss of position in an arm voluntarily held out) with the classic motor response to a painful stimulus that is used to define anaesthetic potency.

Methods and results

The study was approved by the local ethics committee. We studied patients about to have surgery in the gynaecology day case unit. We asked 49 healthy, English speaking women aged over 16 yr to participate: 43 agreed, and gave written, informed consent. Patients were not recruited if they had received any form of sedation or analgesia in the 12 h before the study. We had no preliminary data that could be used to calculate sample size. We randomized patients by flipping a coin to receive either propofol or sevoflurane in an open, parallel, randomized design. As the rate of administration of i.v. agents affects the apparent potency of the agent, we gave each patient the agent at a rate proportional to the dose appropriate for that patient. We estimated the induction dose of thiopental, using the regression equation of Avram: 

\[
\text{Dose of thiopental (mg)} = 295 + \text{weight (kg)} - \text{Age (yr)} \times 1.86
\]

The estimated induction dose of propofol was calculated using a potency ratio of 0.53 for propofol. We then took 2.5 times this dose, made up to 50 ml using saline 0.9%, and gave it from a Graseby 3500 syringe driver set to run at 720 ml h\(^{-1}\). In this way, the estimated induction dose should have been given in 100 s. The injection continued until all the end-points had been reached or the whole syringe had been given.

The method of induction with sevoflurane did not require the patient to change her breathing. We added sevoflurane 0.5% to the fresh gas flow, which was oxygen 3 litre min\(^{-1}\). After three breaths, the sevoflurane concentration was doubled to 1%, doubled again after another three breaths, and so on until the maximum concentration of 8% was reached. This level was then maintained until all the end-points had been reached.

The patients were monitored with ECG, non-invasive arterial pressure, and pulse oximetry. Arterial pressure readings were not taken during induction of anaesthesia. During induction, the patient breathed from a co-axial Mapleson D circuit fitted with a side stream carbon dioxide analyser (Datex Cardiocap II). Movements of the reservoir bag and a carbon dioxide trace showing a secondary peak during inspiration indicated rebreathing of the exhaled gas.

Each patient lay supine on a horizontal table. A vein on the dorsum of the left hand was cannulated. Two adhesive silver/silver chloride foil electrodes (Silver Mactrode Plus, Marquette Medical Systems) were applied, one on each side of the proximal phalanx of the right ring finger, avoiding contact between them. These were connected to the output of a peripheral nerve stimulator (Innervator NS242, Fisher and Paykel). Before breathing from the mask was started, the right arm was held raised and straight, at 45% to the horizontal and away from the side of the patient.

During the induction process, after the patient had closed her eyes and the breathing pattern had changed, we applied a stimulus to the finger (40 mA, 50 Hz, for 2 s), timed to occur every 15 s from the start of anaesthetic administration, until no motor response occurred. A motor response was defined as any movement of the limbs, occurring within 5 s of the stimulus. When all the end-points were reached or after the entire i.v. dose had been given, the study was stopped and anaesthesia continued as appropriate clinically. If the entire dose of propofol was given without all the end-points having occurred, only those end-points that had been reached were analysed.

We used Minitab v.13.1 for statistical analysis. Data were tested for normal distribution using the Anderson–Darling test. The data were displayed visually as cumulative effect against administration time, and are summarized as median and quartiles. The coefficient of variation of the induction times was taken as an index of the slope of the time–response curve. We compared the homogeneity of these coefficients with a method that allows comparison of variances. Significance was set at \( P < 0.05 \).

We plotted a cumulative response–log time curve for each response, using logit values for the proportion of patients that had reached the end-point. These were fitted using weighted linear regression, ignoring values with large standardized residuals. The plot was used to illustrate the
relationships and predict the ED₅₀ for abolition of movement with propofol.

Of the 43 patients admitted to the study, five were withdrawn for incidental reasons, such as changes in the organization of the operating list. Data from 19 patients in each group who yielded results are presented (Table 1). The two groups were very similar in age, height, and weight. No apnoea, coughing, or excitement occurred in patients induced with sevoflurane.

The end-point of arm descent occurred early during the administration of both agents (Table 1). The median time was less with propofol (65 s) than for sevoflurane (105 s). The abolition of movement by sevoflurane occurred at 226 s, and with more variation (interquartile range, 131 s) compared with the loss of arm tone (interquartile range 33 s).

In contrast, eight of the patients who received propofol continued to respond to the electrical stimulus after the entire i.v. dose of 2.5 × ED₅₀ had been given. For sevoflurane, the distribution of the times to loss of arm tone and response to a painful stimulus were not significantly different from normal. For propofol a single outlier, with a time of 125 s, made the distribution of values for the loss of arm tone significantly different from normal ($P=0.036$). Without this value, the distribution did not differ from normal. The variances of the propofol and sevoflurane times for loss of tone were not significantly different (Fig. 1).

**Comment**

The median time to arm descent was less with propofol than for sevoflurane. Propofol abolished arm tone more rapidly than we had expected. We had planned to give an estimated ED₅₀ in 100 s, so that we could reasonably compare the times for propofol and sevoflurane. The data used to estimate the ED₅₀ were based on an end-point of drop of a weight, which occurs before arm drop.² Induction time could have been reduced by the combination of a slow injection and dilution. Both of these factors increase the apparent potency.⁴

The onset of the effect of sevoflurane is delayed, because the method we used delayed the breathing of effective concentrations of the agent. After this, in the time taken for this study, the alveolar concentration of sevoflurane is likely to be increasing almost linearly. The small fresh gas flow will also reduce the rate of uptake so that alveolar concentration will increase more slowly and thus more linearly over this limited time. The time constant for brain wash-in will depend on the brain–blood partition coefficient, which is 1.7,⁷ and brain sevoflurane concentration will lag behind the blood concentration. The increase in brain concentration is also likely to be approximately linear over the time that these measurements were made. Reliable inhalation induction without apnoea is possible if fresh gas flows are reduced.³

Response to pain was not lost in eight of the 19 subjects receiving propofol, so satisfactory estimates of the variance could not be made. The fitted curve was constructed using logit values from the patients who did reach the end-point. This predicted a median time to loss of response of 230 s and the lower quartile of the distribution was 129 s (Fig. 1).

The cumulative effect-log time curves appeared sigmoid and this was confirmed by the logit plots. In studies such as this, other factors affect the drug response as well as the

---

**Table 1** Patient details and results. The time to reach each end-point is given. The median time for propofol to abolish response to pain is predicted. The upper quartile value is not given because this end-point was not achieved in nine patients.

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Arm drop (s)</th>
<th>Move (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol (n=19)</td>
<td>Mean</td>
<td>30</td>
<td>165</td>
<td>64</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>sd (range)</td>
<td>9 (19–51)</td>
<td>9</td>
<td>Median</td>
<td>65</td>
</tr>
<tr>
<td>Sevoflurane (n=19)</td>
<td>Mean</td>
<td>29</td>
<td>165</td>
<td>65</td>
<td>Quartiles</td>
</tr>
<tr>
<td></td>
<td>sd (range)</td>
<td>10 (18–45)</td>
<td>8</td>
<td>Quartiles</td>
<td>88–121</td>
</tr>
</tbody>
</table>

---

![Fig 1](image) Cumulative numbers of patients achieving the end-points, in relation to time after starting administration of the agent. (A), propofol, (B) sevoflurane. Square symbols, loss of arm tone; circles, loss of response to painful stimulus. The solid lines were fitted using weighted logit linear regression.
mass administered.4,8 We compared the coefficient of variation of the responses, because the mean time to achieve the responses differed. There was no significant difference in the variance of the time to cause loss of arm tone between the agents. Our findings for the loss of tone, with propofol and sevoflurane, support a previous study of several measures of loss of consciousness, all of which can be loosely considered to indicate obtunding effects (breathing pattern, voluntary movement, weight drop, and arm tone).5 We also found that the plots for loss of tone and loss of response to pain for propofol, were dissimilar. This is a well recognized feature of propofol.9 Many consider volatile anaesthetic agents have similar dose–response curves for actions such as loss of consciousness and loss of motor response to pain, but data to support this belief are limited.10 The additional information provided by this study, using a continuous process of inhalation induction, is valuable confirmation of the similarity.

Despite the simple method we used, comparison of different end-points for a single drug are valid, because the drug effect was progressively increasing. Inhaled agents should ideally be compared using a variety of clinically relevant end-points and in steady state conditions.7,11 However, the simple method we describe can demonstrate dissimilar responses.

References