Do anxiety or hypocapnia predispose to apnoea after induction of anaesthesia?†

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Summary
We have studied the incidence of apnoea after induction of anaesthesia in patients allocated randomly to receive a standardized dose of either propofol or etomidate. We measured anxiety before operation with a standard questionnaire and end-tidal carbon dioxide concentration from a mask during breathing 35% oxygen, before induction of anaesthesia. Respiration was measured by pneumotachograph and impedance pneumograph. There was no significant relationship between anxiety score and end-tidal carbon dioxide concentration before operation. Patients given propofol (n=26) received a median dose of 157 mg over 70 s, and 17 became apnoeic (median duration 24 s, quartile values 0, 76). Apnoea was more severe in patients whose preoperative end-tidal carbon dioxide value was less than the median value (median duration of apnoea 61 s compared with 10 s; P<0.05). Patients given etomidate (n=25) received 16.2 mg in 57 s, which was a significantly smaller fraction of the calculated dose requirement, and had significantly less apnoea: eight became apnoeic (median duration 0 s, quartile values 0, 23 s). There was no relationship between apnoea and end-tidal carbon dioxide concentration in these patients. Anxiety did not relate to the incidence of apnoea with either induction agent. We conclude that apnoea after induction of anaesthesia with propofol is more likely if hypocapnia is present but we could not relate apnoea or hypocapnia to anxiety in the ward before operation. (Br. J. Anaesth. 1997; 78: 153–156)

Key words

Patients and methods
After obtained local Ethics Committee approval and written informed consent, we studied women undergoing gynaecological procedures under general anaesthesia as day patients. We excluded patients who were more than 40% of their expected weight, had clinically significant cardiorespiratory disease or who were receiving medication that could alter anxiety or respiratory responses. We did not exclude those who were in early pregnancy. Between 30 min and 2 h before the anaesthetic, we assessed each patient’s anxiety using a standardized questionnaire consisting of 12 statements, with the response to each question graded from “not at all” to “extremely” in five categories. The statements were both positive (e.g. “I feel I can cope”) and negative (e.g. “I want to escape from here”) so that the categorical response required more careful thought. The categories were marked from 1 (least anxious) to 5 (most anxious) and summed so that the score was between 12 (least anxious) and 60 (most anxious).

To allow anaesthetic induction to be as standard as possible, and compare the induction agents, we estimated the induction dose required for each patient so that by giving this estimated dose at a steady rate each patient should receive an induction dose of the agent over the same time. We noted height and weight of the patients and measured skinfold thickness at the biceps, triceps, subscapular region and suprailliac regions with standard methods to allow estimation of lean body mass. Using age preoxygenation may be encouraged to hyperventilate or may hyperventilate because they are anxious, and hence become hypocapnic. We tested the hypothesis that anxiety and hypocapnia before operation would predispose to apnoea and studied the effects of two agents that are known for their different effects on respiration, propofol which causes more apnoea¹ and etomidate less, in comparison with other agents.⁴

Apnoea is frequent after introduction of anaesthesia with i.v. agents, and more likely with propofol than with other agents.¹ Propofol depresses the ventilatory response to hypoxia,² but in some circumstances apnoea can also be caused by a combination of hypocapnia and sedation: for example it can be caused by voluntary hyperventilation in association with nitrous oxide inhalation.³ Patients receiving

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and lean body mass we predicted the clinical induction dose of thiopentone using regression data from Avram and co-workers, with the equation:

\[
\text{dose (mg)} = 282 + 1.6 \times \text{Lean mass (kg)} - 1.78 \times \text{Age (yr)}
\]

From this thiopentone dose, the equivalent induction dose for propofol was obtained using a relative potency of 0.625. For etomidate we used a ratio of 0.038. These doses of propofol and etomidate, given over 100 s, provide a median induction dose for similar patients (unpublished data). We diluted 1.4 times the estimated induction dose in 40 ml, with 0.9% sodium chloride containing 1 ml of 0.5% lignocaine solution. At induction of anaesthesia this was given as 0.4 ml s\(^{-1}\) so that a median induction dose was given in approximately 70 s and further agent was available in the syringe if necessary for patients who required more than the median amount. Randomization was with sealed envelopes in blocks of 20.

No premedication was given. When the patient came to the anaesthetic room an i.v. cannula was inserted in one hand and a two-electrode impedance pneumograph was attached using disposable silver–silver chloride ECG electrodes placed on each side of the chest in the midaxillary line at the level of the nipples. Standard electrodes for ECG monitoring, non-invasive arterial pressure cuff and a finger probe pulse oximeter were attached. No arterial pressure measurements were made during the measurements. A well fitting mask, with an inflatable pneumatic rim (Respironics), was applied to the face and the patient’s head extended to allow a clear airway to be maintained. The mask was fitted with a sampling port which was connected to a sidestream capnometer (Datex OxyCap), calibrated at the start and end of the study with the manufacturer’s standard gas. The mask was connected to a pneumotachograph and a T-piece system supplied with a Venturi oxygen device that gave 35% oxygen: the other limb of the T-piece was open to room air. Pneumotachograph pressure was measured with a differential transducer (Furness micromanometer) and the flow and pneumograph signals passed to a laptop computer for digitizing and storage using a commercial logging and analysis package (Oxcams Cardas). The patient was then given a solid steel cylinder, 10 cm long and 1.25 cm in diameter, to hold between the thumb and first finger of the hand that did not have the i.v. cannula, and asked to hold it without letting it drop.

After the patient had been breathing from the system for approximately 2 min she was asked to exhale to obtain a good expiratory plateau value for end-tidal carbon dioxide concentration and this value was noted. When respiration had become regular again and satisfactory signals of flow and pneumograph were present on the computer display, the induction agent was injected at 0.4 ml s\(^{-1}\) until the patient dropped the weight, when injection stopped and the time was recorded on the computer. If there was no flow signal, then the mask was kept in place until respiration re-started. The impedance signal was observed to see if there was obstructive apnoea, with absent flow but continued chest wall movements, in which case the head and neck were moved to obtain a clear airway. The mask was kept in place until respiration re-started and then removed to allow the anaesthetic to be continued. The digitized record was replayed later. Apnoea was defined as the absence of inspiratory flow for more than 10 s: if apnoea occurred, the times of cessation and restarting respiration were noted. Summary values for apnoea duration in the groups were calculated using zero values for those subjects who did not stop breathing.

After the patient had returned to the ward, another measurement was made of end-tidal carbon dioxide concentration between 1 and 2 h after the procedure. Analgesics used in the operative and postoperative periods, which were not standardized, were noted.

The relationship between the incidence and duration of apnoea, preoperative anxiety score, end-tidal carbon dioxide concentration and induction agent was investigated with scatter plots. The incidence of apnoea was tested using the chi-square test and the severity of apnoea compared between agents, and within subgroups, using the Mann–Whitney test, with Minitab version 8.2 running in MS-DOS version 6.2. \(P<0.05\) was taken as significant. The distribution of many of the variable values was not normal and they are summarized as median (interquartile) values.

**Results**

Of 56 patients who agreed to the study, 54 were allocated randomly to treatment (six were asked and declined to take part). Patient details are shown in table 1. There were no differences between groups in age, height, weight, percentage body fat, preoperative anxiety scores or end-tidal carbon dioxide values.

The median dose of propofol given was 158 (140,182) mg and induction time was 67 (59,77)s. This was significantly greater than the induction time for the etomidate group (57 (48,64) s; dose administered 16 (14.5, 17.6) mg). Because the agents were given at a rate set by the predicted dose for each patient, the different induction times indicate a significant difference between the proportion

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient details (median (quartile values) or numbers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>Propofol group</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>26 (28–39)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160 (158–163)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64 (60–70)</td>
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<tr>
<td>% Body fat</td>
<td>37 (34–40)</td>
</tr>
<tr>
<td>Anxiety score</td>
<td>23 (18–29)</td>
</tr>
<tr>
<td>Preoperative end-tidal CO(_2) (kPa)</td>
<td>4.4 (4.3–4.7)</td>
</tr>
<tr>
<td>Dose prediction (mg)</td>
<td>181 (173–187)</td>
</tr>
<tr>
<td>Dose administered (mg)</td>
<td>158 (141–182)</td>
</tr>
<tr>
<td>Dose given/dose predicted</td>
<td>0.87 (0.78–1.05)</td>
</tr>
<tr>
<td>Induction time (s)</td>
<td>67 (60–77)</td>
</tr>
<tr>
<td>Apnoea (s)</td>
<td>17</td>
</tr>
<tr>
<td>Apnoea (s) (all patients)</td>
<td>24 (0–77)</td>
</tr>
<tr>
<td>Postoperative end-tidal CO(_2) (kPa)</td>
<td>4.7 (4.1–5.5)</td>
</tr>
</tbody>
</table>
of predicted dose given; for propofol 0.87 (0.77–1.05) and for etomidate 0.75 (0.66, 0.83) (P<0.01).

There was no relationship between preoperative anxiety score and end-tidal carbon dioxide values before operation.

There was a significant difference in the incidence and duration of apnoeas in patients who received propofol (17 apnoeas, median duration of apnoea 24 (0, 77) s) compared with the etomidate group (eight apnoeas, median duration 0 (0, 23) s) (P<0.05). Figure 1 shows the relationship between apnoea duration and preoperative end-tidal carbon dioxide values. Because the relationship between these values was not linear, we classified patients into those whose preoperative end-tidal carbon dioxide concentration was greater, and less than or equal to the median: we then compared duration of apnoea in the low and high end-tidal carbon dioxide groups. In patients who received propofol, apnoea was significantly greater in the 13 patients who had smaller carbon dioxide values (61, 18–146 s) compared with those who had larger carbon dioxide values (10, 0–40 s) (P=0.0167). This relationship was not found in patients who received etomidate (0, 0–41 and 0, 0–14 s for the two groups, which contained 12 and 13 patients, respectively) (P=0.767).

Most patients received a variety of analgesics, including long- and short-acting opioids, either during or after the procedures, and no relationship was found between postoperative end-tidal carbon dioxide values or changes in values before and after operation, with any other variable. Postoperative values were obtained 25–95 min after recovery from anaesthesia. One value could not be obtained for technical reasons, but for the remainder, median end-tidal carbon dioxide values after operation were 4.8 (4.2–5.3) kPa whereas they were 4.4 (4.1–4.7) kPa before the procedure (P<0.01). There was no difference in carbon dioxide values after operation in patients who received propofol and those who received etomidate.

Discussion

Apnoea is less frequent when propofol is given slowly whereas slow injection of other induction agents does not seem to affect the incidence of apnoea. As we wished to compare the two agents, we used a method that should have allowed us to give the induction dose of both agents in the same time. We used estimates of potency derived in the same type of patient, where the induction dose was given over approximately 80 s. Injection time was decreased slightly in this study to approximately 70 s. We did so to more closely simulate the rate of injection that is used commonly in clinical practice and we wished to allow apnoea to become apparent so that we could investigate the relevant factors associated with it. However, the estimates were greater than necessary, significantly so for etomidate, and therefore the injection times were significantly different. However, the differences were small (12% of the dose estimate) and we do not consider that the difference in time taken for injection (57 vs 66 s) affected the comparability of the effects of the agents, particularly as both were given to the same end-point.

We used preoxygenation to avoid the confounding effect of hypoxia, which may contribute to restoration of breathing after apnoea has occurred, but avoided using 100% oxygen because it may alter cerebral blood flow and thus affect respiration. Although propofol depresses the ventilatory response to hypoxia there are no definitive reports that preoxygenation can prolong the duration, of apnoea caused by propofol, and a decrease in ventilation in response to hyperoxia can be found to persist during propofol anaesthesia. The depressant effects of propofol on ventilatory responses to carbon dioxide are also significant and prolonged. Consequently, our finding that propofol caused apnoea, and etomidate did not, was expected, and we have concentrated on the features of the apnoea in this group of patients.

We have used the questionnaire for anxiety in previous studies and found it satisfactory. As suggested by Millar and co-workers, it describes anxiety in terms that most patients find familiar. These workers found three different methods of measurement of equivalent efficacy, and we consider that our questionnaire is similar. However, we found that anxiety measured in this way could not be related to preoperative end-tidal carbon dioxide concentration or to the incidence of apnoea. Anxiety may have increased between completing the form and starting the induction of anaesthesia, to a different degree in different subjects, thus invalidating this measure as a test of the initial hypothesis.

We measured end-tidal carbon dioxide using a mask, which is less accurate than the use of a mouthpiece, but we were able to assess the size of the expired breath and are confident that measurements in these relatively young and healthy subjects were a good index of PaCO₂. However, we did not control or standardize analgesic administration (which varied considerably according to the procedure undertaken) and hence are not confident that the values of
end-tidal carbon dioxide that we obtained after operation were of value, although we had hoped that the change from before to after operation could have been an index of those patients who were hypocapnic before the procedure, by relating the carbon dioxide value to their resting value.

There was no clear linear relationship between preoperative carbon dioxide concentration and apnoea. However, it was evident that hypocapnia was associated with more frequent and prolonged apnoea after propofol, whereas the less frequent apnoeas after etomidate could not be related to hypocapnia. We propose that the drive to respiration from wakefulness and anxiety have reduced arterial and brain carbon dioxide values well below those necessary to stimulate respiration, and after loss of consciousness these values have to increase sufficiently before regular respiration starts again. We attempted to minimize upset to the patient from the use of the mask, and it is likely that the effects were similar to a routine anaesthetic, and consequently we are confident that our findings reflect the clinical situation. Although other manoeuvres have been suggested as helpful in reducing the likelihood of apnoea after induction of anaesthesia, such as slow administration of propofol and vital capacity breaths before induction, we suggest that manoeuvres to limit the development of hypocapnia may be useful if apnoea is troublesome.

Acknowledgements

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References