Ventilatory effects of eltanolone during induction of anaesthesia: comparison with propofol and thiopentone†

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Summary

We recorded the ventilatory effects of eltanolone 0.75 mg kg\(^{-1}\), propofol 2.5 mg kg\(^{-1}\) and thiopentone 4 mg kg\(^{-1}\) at induction of anaesthesia in 76 unpremedicated patients, aged 18–65 yr. Measurements were made using a pneumotachograph incorporated between a close-fitting face mask and a T-piece delivering 35 % oxygen. Eltanolone caused significantly less apnoea than propofol (incidence 57 % vs 100 %) and less reduction in ventilation than propofol (median maximum decrease 4.8 vs 7.8 litre min\(^{-1}\) ), but the differences between eltanolone and thiopentone were smaller and generally not significant. Ventilatory frequency was maintained well in the eltanolone group. (Br. J. Anaesth. 1996; 77: 194–199).

Keywords


The anaesthetic properties of some steroids have been recognized for more than 50 yr [1]. However, the development of these compounds for clinical use has been slow, because of adverse events with water-soluble agents [2–4] and the lack of a suitable solvent for lipid-soluble agents.

Eltanolone (3α-hydroxy-5β-pregnane-20-one, pregnanolone) has been known as a potent anaesthetic since 1957 [5]. An emulsion formulation of eltanolone, with the agent dissolved in the lipid phase of an oil–water emulsion, is now available (Caretan, Pharmacia). Potential advantages of this new drug, in comparison with currently available induction agents, include a high therapeutic ratio and lack of pain on injection. In addition, preliminary studies have reported less apnoea [6, 7], in keeping with findings with earlier steroid induction agents [8, 9].

Lack of depression of ventilation is advantageous in anaesthesia if neuromuscular blocking agents are not used, allowing smooth transition from i.v. to inhalation anaesthesia and helping to prevent hypoxia. The aim of this study was to investigate the ventilatory effects of eltanolone at induction of anaesthesia, and to compare these effects with those of propofol and thiopentone.

Patients and methods

After obtaining local Ethics Committee approval and written informed consent, we studied 76 ASA I and II patients, of both sexes, aged 18–65 yr, undergoing elective surgery. We excluded patients who were more than 50 % above ideal weight for height (Metropolitan Life Insurance Company tables), pregnant, who had significant respiratory disease, anaesthetic drug allergy, who abused alcohol or other substances or who were receiving any medicines which might affect ventilation. Patients received no premedication and were allocated randomly to receive eltanolone 0.75 mg kg\(^{-1}\), propofol 2.5 mg kg\(^{-1}\) or thiopentone 4 mg kg\(^{-1}\) for induction of anaesthesia. These doses have been shown to be approximately equipotent [7, 10].

After arrival in the anaesthetic room an i.v. cannula was inserted. Inductance bands were positioned around the chest and abdomen and connected to a respiratory inductance plethysmograph. The signals, representing dimensional changes in the rib cage and abdomen with respiration, were recorded using commercial respiratory monitoring software (Cardas, version 2.07 advanced, Oxcams, Oxford), running in MS-DOS (version 6.20), onto a lap-top computer. These bands allowed detection of upper airways obstruction by comparison of chest wall movement and expired volumes. Patients lay on a mattress filled with polystyrene beads that was made rigid to prevent body movement (Vac-Pac, Howmedica). Patients breathed 35 % oxygen from a T-piece, through a screen pneumotachograph (F100L, Mercury Electronics) and a tight-fitting face mask with a wide pneumatic seal (Downs CPAP mask No. 9002, Vital Signs Inc., NJ, USA), held in place with both hands by the anaesthetist. The pneumotachograph was connected to a differential pressure transducer (± 10 mm H\(_2\)O, Furness) and the resulting flow signal was also recorded. The system was calibrated in the laboratory using a series RT200 calibration analyser (Timeter Instrument Corporation, Missouri, USA) and was linear up to 40 litre min\(^{-1}\). Immediately before each study, the
calibration was checked against a flowmeter (its accuracy had also been verified in the laboratory) and was considered acceptable if the error was less than ± 5%. A pulse oximeter (Ohmeda Biox 3700) was used to measure oxygen saturation and heart rate and these signals were also recorded on the computer.

After a period of 3–5 min of stable breathing, the induction agent was administered over 30 s. Lignocaine 10 mg was mixed with propofol to prevent pain on injection. The moment of loss of consciousness was noted from when the patient dropped a metal rod held between the thumb and index finger. If consciousness was not lost within 120 s further anaesthetic was given and the patient was withdrawn from the study. The patient’s jaw was supported gently by the anaesthetist to prevent upper airway obstruction. Recordings were continued for 4 min from the start of induction or until the patient showed signs of arousal when a further dose of induction agent was administered. Any adverse events which occurred, including apnoea, were noted. After completion of this study, anaesthesia was continued as appropriate for clinical management. A tracing of part of a typical study is shown in figure 1.

The flow signal was then analysed by a locally written computer program which calculated breath values for tidal volume ($V_T$), respiratory frequency ($f$), inspiratory time ($T_I$) and expiratory time ($T_E$). Mean values over 30 s were calculated every 30 s from the start of administration of the induction agent. Minute ventilation ($V_E$) was then obtained from the product of $V_T$ and $f$. A stable 30-s period, approximately 2 min before the start of induction, was used to calculate control values.

Adverse events during anaesthesia were noted. All patients were visited approximately 24 h after operation and returned a questionnaire 2 weeks later to determine if any side effects had occurred. They were asked specifically about the severity and duration of nausea and vomiting, dizziness or lightheadedness, headaches, sore throat, rashes or drip site inflammation, muscle pains and cough.

Data were analysed using the Minitab statistical package (release 8.2), running in MS-DOS (version 6.20). Non-parametric tests of significance were used to compare the three groups and changes from baseline (Kruskal–Wallis, Mann–Whitney, Wilcoxon signed rank sum and chi-square as appropriate). With 23 patients per group the estimated power of the study to detect a difference in ventilation of 2 litre min$^{-1}$ at a significance level of 0.05 was 0.8.

## Results

Of the 76 patients recruited, results were available for analysis from 69, 23 per group. Two patients in the propofol group were excluded because of study violations, two patients (one eltanolone, one propofol) developed upper airway obstruction after induction of anaesthesia, shown by normal or increased chest wall movements with absent or reduced flow, and therefore were excluded, data from two patients in the thiopentone group could not be analysed because their breathing patterns were too irregular, and one patient’s operation was cancelled after randomization to receive eltanolone.

The characteristics of those included are shown in table 1. The propofol group contained more males and the thiopentone group more females than the eltanolone group, with a corresponding bias in height and weight.

Induction of anaesthesia was successful in all patients, and the time from the start of administration of the induction agent to loss of consciousness was similar in the three groups (means 45.8, 43.5 and 45.3 s in the eltanolone, propofol and thiopentone groups, respectively).

The incidence of apnoea and the median duration of absent breathing are shown in table 2. Differences

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**Table 1** Patient characteristics (mean (SD or range) or number)

<table>
<thead>
<tr>
<th></th>
<th>Eltanolone (n = 23)</th>
<th>Propofol (n = 23)</th>
<th>Thiopentone (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>37.1 (18–58)</td>
<td>37.5 (22–54)</td>
<td>37.3 (20–64)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 (9.4)</td>
<td>175 (8.4)</td>
<td>169 (9.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.8 (9.2)</td>
<td>73.2 (10.5)</td>
<td>65.5 (12.6)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>13:10</td>
<td>16:7</td>
<td>7:16</td>
</tr>
</tbody>
</table>

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**Table 2** Incidence of apnoea and duration of absent breathing in the three groups (number (%) or median (quartiles))

<table>
<thead>
<tr>
<th></th>
<th>Eltanolone (n = 23)</th>
<th>Propofol (n = 23)</th>
<th>Thiopentone (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) apnoeic episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any duration</td>
<td>13 (57)</td>
<td>23 (100)</td>
<td>17 (74)</td>
</tr>
<tr>
<td>&gt; 30 s</td>
<td>7 (30)</td>
<td>17 (74)</td>
<td>9 (39)</td>
</tr>
<tr>
<td>&gt; 60 s</td>
<td>3 (13)</td>
<td>15 (65)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Duration of absent breathing (s)</td>
<td>6 (0, 41)</td>
<td>88 (30, 113)</td>
<td>22 (0, 43)</td>
</tr>
</tbody>
</table>
Respiratory variables for the three groups for each time period (median (quartiles)). Statistical differences (\(P < 0.05\)) between drug groups are indicated (*eltanolone vs propofol, †eltanolone vs thiopentone). All values of minute volume and tidal volume were significantly reduced from baseline from 60 s onwards. Frequency was reduced significantly from baseline at 60–120 s in the propofol group, and at 60–90 s in the thiopentone group. From 150 s in the eltanolone group, 180 s in the propofol group and at 240 s in the thiopentone group, ventilatory frequency was significantly greater than baseline.

Table 3 summarises the adverse events during anaesthesia. Involuntary movement occurred in 10 patients who had received eltanolone and in four who had received propofol. These were graded as moderate in three of the eltanolone group and mild in the remainder. They lasted between a few seconds and several minutes, terminated spontaneously in all patients who had received eltanolone and propofol groups were highly significant (\(P < 0.01\)) but differences between the eltanolone and thiopentone groups were not.

Table 3 shows the respiratory variables measured. Baseline ventilation and tidal volume were greater in patients who received propofol, probably because of the preponderance of males in this group. In all groups there was a significant reduction from baseline in both minute volume and tidal volume from 60 s onwards. The maximum reduction in minute ventilation in the eltanolone group was significantly less than that in the propofol group (median 4.8 vs 7.8 litre min\(^{-1}\)), but was not significantly different from the thiopentone group (6.1 litre min\(^{-1}\)). Similarly, tidal volumes were depressed to a greater extent in the propofol group.

Ventilatory frequency, however, exhibited a somewhat different pattern. In the eltanolone group it did not decrease below baseline values, unlike the propofol and thiopentone groups where it was significantly below baseline at 60–120 s and 60–90 s, respectively. The difference between eltanolone and propofol was significant at 60–150 s. In all groups ventilatory frequency increased above baseline towards the end of the study and this effect was most marked in the eltanolone group and least in the thiopentone group.

We also analysed the minimum value of minute ventilation in each patient after injection. The median minimum minute ventilation was 3.3 litre min\(^{-1}\) (interquartile range 0–4.5 litre min\(^{-1}\)) in the eltanolone group, 0 (0–0.6) litre min\(^{-1}\) in the propofol group and 0.7 (0–2.4) litre min\(^{-1}\) in the thiopentone group. The minimum minute ventilation tended to be reached later in the eltanolone group (median 90 s from the start of injection) than in the two other groups (median 60 s). The difference in treatment effect between eltanolone and propofol was highly significant (\(P < 0.01\)), but the difference between eltanolone and thiopentone was not (\(P = 0.09\)).

Summary spiromgrams have been drawn to allow comparison of the pattern of breathing after each drug, using baseline measurements and values at 180 s (fig. 2). This time period was chosen for analysis because it was the first after injection where spontaneous respiration had restarted in most patients. Inspiratory time (\(T_I\)) was reduced more in the eltanolone and propofol groups at 180 s compared with the thiopentone group (\(P < 0.05\)), corresponding to the increase in ventilatory frequency observed in these patients. Inspiratory time was expressed by the gradient of the inspiratory line (\(V_T/T_I\)), was reduced more in the propofol group than in the eltanolone or thiopentone groups, but this difference was not significant.

There were no serious adverse events during the study, but several minor side effects were noted. Table 4 summarizes the adverse events during anaesthesia.
cases and did not cause any clinical difficulty. Additionally, two patients in the eltanolone group developed hypertonus of the neck or upper limbs.

Flushing occurred in two patients in the eltanolone group and in one patient in each of the other treatment groups. However, in all cases this occurred after the end of the study and was related temporally to the administration of other drugs known to release histamine rather than administration of the induction agent.

Six patients who had received eltanolone coughed during the anaesthetic, compared with two who had received propofol and three who had received thiopentone. Additionally, one patient in the eltanolone group developed laryngospasm and one patient in the propofol group developed bronchospasm. However, these adverse events were not generally attributable to the induction agent, but usually occurred if the inspired concentration of isoflurane was increased rapidly. Oxygen saturation decreased to less than 85% as a result of coughing in one patient after propofol, and because of prolonged apnoea in five patients who received propofol and one patient who received thiopentone.

Tachycardia (>100 beat min⁻¹) was more common after eltanolone, occurring in 10 patients compared with only two after propofol and none after thiopentone. However, this was probably directly attributable toeltanolone in only two cases, with insufficient depth of anaesthesia and other anaesthetic agents being more likely causes in all other cases.

Adverse events reported after operation are shown in table 5. Nausea and vomiting were the most frequently described side effects, with a greater incidence reported in the eltanolone and thiopentone groups than in the propofol group, but the differences were not significant. Similar numbers of patients in each group complained of dizziness,
while the incidence of all other side effects was low and distributed fairly evenly between the three groups.

Discussion

Our results confirmed that induction of anaesthesia with eltanolone in unpremedicated patients produced much less depression of ventilation than an equipotent dose of propofol, in terms of reduction of minute volume, incidence of apnoea and duration of absent breathing. Ventilatory depression with eltanolone was also less than that with thiopentone, but this was significant only at 60 s, with no significant difference in either the maximum reduction or minimum minute ventilation recorded. Ventilatory frequency was better maintained with eltanolone than with either of the two drugs, and was increased significantly from baseline from 150 s onwards.

A larger sample size might have revealed a difference between eltanolone and thiopentone. When we designed the study we calculated that a sample size of 69 would give a power of 0.8 to detect a difference of 2 litre in minute ventilation, at a significance level of 0.05, given an SD for ventilation of 2.2 litre min$^{-1}$. However, there was considerable variation in the reduction of ventilation, and the power of the study to detect a real difference in ventilation of 2 litre min$^{-1}$ was only approximately 0.75.

We found that the baseline value of minute volume was significantly greater in the propofol than in the eltanolone and thiopentone groups (median 8.2 vs 7.9 and 7.2 litre min$^{-1}$, respectively). This was probably because of the difference in sex distribution between the three groups, and we do not consider the difference to be clinically important.

In any study of ventilation using a face mask there is potential for measurement error for several reasons. Unrecognized mask leaks are one possible source of inaccuracy. To minimize this we used a face mask with a wide pneumatic rim, applied water soluble jelly to improve the seal if facial stubble was present, and held the mask firmly in place using two hands, allowing manual detection of escaping gas. Use of an end-tidal carbon dioxide monitor in a few patients showed normal waveforms and end-tidal values, confirming our belief that significant gas leaks did not occur. The measurement apparatus may itself induce changes in ventilatory pattern [11], but this effect is least when a face mask with high fresh gas flow is used, as in our system, and is less relevant when comparing groups as all patients would be equally affected. We did not make any recordings of arterial pressure during the study as we believe that inflation of a pneumatic cuff on the arm may have been sufficiently stimulating to affect respiratory pattern.

Further investigation of eltanolone may provide different estimates of the relative potency, which could alter the interpretation of our results. Also, although administration of a pre-calculated bolus dose of induction agent over approximately 30 s is common clinical practice, other methods, for example less rapid administration to a clinical end-point such as cessation of counting, could result in different dose requirements and ventilatory effects [12–14].

Direct comparison of our results with other studies is difficult because of both the variable doses administered and the different premedications used in earlier work. Additionally, our study is the first which has been designed to examine specifically the ventilatory effects of eltanolone, and therefore the only previous eltanolone data available for comparison are observations of apnoea.

Using eltanolone 0.75 mg kg$^{-1}$ we found that 30% of patients were apnoeic for greater than 30 s, with 13% being apnoeic for more than 60 s. This is a greater incidence than reported by many earlier authors [6, 7, 15, 16] but, except for one study [16], smaller doses of eltanolone were used. After a prior dose of fentanyl, and a dose of 0.59–0.89 mg kg$^{-1}$, given over a range of times, Myint, Peacock and Reilly [12] reported that 37% of their patients were apnoeic for more than 30 s. All patients studied by Kallela and colleagues [17] using eltanolone 0.8 mg kg$^{-1}$ were apnoeic for more than 60 s, probably because of the generous dose of alfentanil given before induction.

There are some data available on the ventilatory effects of earlier steroid induction agents, and in general the pattern we have seen with eltanolone is similar. Hall, Whitwam and Morgan [18], using Althesin 50 and 100 μl kg$^{-1}$ after either diazepam or papaveretum premedication, found an incidence of apnoea of 41%, lasting 8–102 s, compared with an incidence of 56.5%, lasting 4–119 s, in our study. Additionally, they described a significant reduction in minute ventilation at 2 and 3 min after induction of anaesthesia with Althesin, with an increase in ventilatory frequency above baseline after 3 min in the non-opioid groups, which are similar to our own observations with eltanolone. However, Campbell and colleagues [19], using Althesin 100–150 μl kg$^{-1}$ in unpremedicated patients, did not observe apnoea, but described a similar increase in ventilatory frequency. Savege and colleagues [8], using Althesin 50 μl kg$^{-1}$, also found an increase in ventilatory frequency after a period of apnoea averaging 23 s. With minaxolone 0.4 mg kg$^{-1}$ [9], a similar picture was seen, with a 25% incidence of apnoea of short duration, an increase in ventilatory frequency in the non-opioid group, and a decrease in minute ventilation.

Our study confirms earlier work suggesting that both propofol and thiopentone are ventilatory depressants [8, 20–23]. However, in general, we demonstrated a greater effect than these earlier studies, in spite of the similar or lower doses we used and the fact that our patients were unpremedicated. The reasons for this are unclear, but the higher frequency of observations which we used, the different measurement techniques and the lower baseline ventilation in some of these studies may all have contributed. Previous reports comparing propofol with thiopentone conflict as to whether or not a difference exists between their ventilatory effects; our results suggest that propofol is a more potent respiratory depressant than thiopentone.
The increase in ventilatory frequency found towards the end of our study when anaesthetic depth was presumably less, is consistent with previous work using a variety of agents [8, 9, 18, 20, 24–26]. The mechanism of this effect is uncertain, but it has been postulated that increased excitability of the inspiratory “off-switch” is responsible [24]. Some steroid hormones are known to be respiratory stimulants [27] which may contribute to the enhanced effect we found with eltanolone; however the similarity of this augmentation to that seen with propofol, when respiration restarts, raises the possibility that the lipid emulsion itself may contribute.

We conclude that the modest ventilatory depression seen after induction of anaesthesia with eltanolone may be useful in allowing a smooth transition to inhalation anaesthesia and may also indicate a role in sedation. The only frequent side effect was involuntary movement, but this was never troublesome and should not affect the value of this new agent.

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References