RESPIRATORY EFFECTS OF ETOMIDATE

M. MORGAN, J. LUMLEY AND J. G. WHITWAM

SUMMARY

The respiratory effects of etomidate 0.3 mg/kg were studied in patients premedicated with either diazepam and atropine or papaveretum and hyoscine. The incidence of apnoea was 40% in those who received the non-narcotic premedication, compared with 27% in those who received the opiate. Those premedicated with diazepam and atropine showed a significant increase in respiratory frequency which was associated with a significant increase in minute volume 4 min after induction of anaesthesia. No such increase occurred in those premedicated with papaveretum and hyoscine. It would appear that the effects of etomidate on respiration are less than those of other i.v. induction agents, but involuntary muscle movement during induction remains a problem.

Etomidate (R-(-)-ethyl-1 (pentylethyl) 1H-imidazole-5-carboxylate sulphate) is the most recently introduced i.v. induction agent, its pharmacological properties being first described in man by Doenicke and others (1973). Ideally, an induction agent should cause no respiratory depression, and preliminary work by Doenicke and his colleagues (1973) suggested that, at a dose of 0.3 mg/kg, etomidate would induce hypnosis with minimal cardiorespiratory effects.

The present study was undertaken to examine the effect of etomidate on ventilation during routine induction of anaesthesia.

METHOD

Patients undergoing gynaecological surgery and who were free from cardiorespiratory disease were studied. They were allocated randomly to receive either diazepam and atropine or papaveretum and hyoscine on a weight basis in the following manner:

less than 60 kg: diazepam 10 mg or papaveretum 10 mg and hyoscine 0.2 mg
60-70 kg: diazepam 15 mg or papaveretum 15 mg and hyoscine 0.3 mg
more than 70 kg: diazepam 20 mg or papaveretum 20 mg and hyoscine 0.4 mg

The diazepam was given orally and all other drugs i.m. 1 h before induction of anaesthesia. All patients receiving diazepam were given atropine 0.6 mg.

An indwelling needle was inserted into a large vein near the elbow because of the high incidence of pain which occurs when etomidate is injected into small veins on the dorsum of the hand (Holdcroft et al., 1976). A face mask was applied and the patient allowed to breathe air through a Dräger non-re-breathing valve. The expiratory port of the valve was connected to a spirometer designed to measure expired volume breath-by-breath (Chakrabarti, Selman and Whitwam, 1977). Part of a typical trace of expired volume is shown in figure 1. The recording system was calibrated with a large syringe, for volumes up to 1 litre.

Expired volume was recorded for a period of 3-4 min before induction of anaesthesia. Etomidate 0.3 mg/kg was then injected over a period of 30 s and observations were continued for 4 min after the start of the injection. Anaesthesia was then continued with an inhalation agent. If any patient developed respiratory obstruction observations were discontinued and measurements were discarded. The incidence and severity of any involuntary muscle movements during induction were noted.

The respiratory rate and minute volume were calculated for the minute before the start of the injection (control) and subsequently each minute for 4 min and the mean values were compared with those in the control period. The incidence and mean duration of apnoea were determined also.

RESULTS

Observations were commenced on 70 patients, 10 of whom developed partial respiratory obstruction so that data from only 60 patients were analysed. Thirty patients received diazepam and atropine as premedication and 30 papaveretum and hyoscine. Four patients who were given diazepam and atropine regained consciousness during the 4th minute after induction of anaesthesia, so that the results at this time in this group relate to 26 patients. There were no significant
differences in the mean ages and weights in each group, nor in the respiratory rates and minute volumes in the control period.

In the majority of patients, towards the end of injection of etomidate there was a brief period of hyperventilation which was followed by a period of respiratory depression, and in some patients apnoea.

**TABLE I. Effect of premedication on the incidence, range and mean duration of apnoea after induction of anaesthesia with etomidate 0.3 mg/kg. Thirty patients in each group**

<table>
<thead>
<tr>
<th>Premedication</th>
<th>Number apnoeic</th>
<th>Incidence (%)</th>
<th>Range</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam + atropine</td>
<td>12</td>
<td>40</td>
<td>13-52</td>
<td>32 ± 14</td>
</tr>
<tr>
<td>Papaveretum + hyoscine</td>
<td>8</td>
<td>27</td>
<td>10-69</td>
<td>27 ± 19</td>
</tr>
</tbody>
</table>

The incidence, range and mean duration of apnoea in each group are shown in Table I. The overall incidence of apnoea was 30%, which lasted for 30 s on average. Twelve (40%) of the patients premedicated with diazepam and atropine developed apnoea, compared with eight (27%) premedicated with papaveretum and hyoscine. This difference was not statistically significant ($\chi^2$ test). Severe involuntary movements during induction occurred in one patient premedicated with papaveretum and hyoscine and moderate movements occurred in another five. None of these patients became apnoeic. In contrast, 12 patients who received diazepam and atropine developed severe involuntary muscle movement during induction and eight of these became apnoeic. Four other patients developed moderate movements and of these two became apnoeic.

The mean respiratory rates and minute volumes in the two groups are shown in table II. Those who received diazepam and atropine showed a highly significant ($P<0.001$) increase in respiratory rate in the 3rd and 4th minutes after induction, but there was no significant change in those premedicated with papaveretum and hyoscine. In the group receiving papaveretum and hyoscine there was a significant reduction in mean minute volume at 2 min, but subsequently this increased, so that at 3 and 4 min the minute volumes were not significantly different from control. In the group receiving diazepam and atropine the mean minute volume was not significantly reduced

**TABLE II. Effect of premedication on respiratory rate (b.p.m.) and expired minute volume ($\dot{V}E$) after induction of anaesthesia with etomidate 0.3 mg/kg (means ± SD). P values refer to comparison with control. Thirty patients in each group**

<table>
<thead>
<tr>
<th></th>
<th>Diazepam and atropine</th>
<th>Papaveretum and hyoscine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate (b.p.m.)</td>
<td>$P$</td>
<td>$\dot{V}E$ (litre)</td>
</tr>
<tr>
<td>Control</td>
<td>16.4 ± 4.45</td>
<td>n.s.</td>
</tr>
<tr>
<td>1 min</td>
<td>16.7 ± 5.56</td>
<td>n.s.</td>
</tr>
<tr>
<td>2 min</td>
<td>17.7 ± 6.18</td>
<td>n.s.</td>
</tr>
<tr>
<td>3 min</td>
<td>20.6 ± 5.32</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>4 min</td>
<td>20.9 ± 4.20</td>
<td>&lt; 0.001</td>
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at any stage and at 4 min was greater than control values \((P<0.05)\).

DISCUSSION

The brief period of hyperventilation occurring in the majority of patients following induction of anaesthesia with etomidate was considerably less than that induced by propanidid, but was similar to that observed after Althesin (Hall, Whitwam and Morgan, 1973). Apnoea occurred most frequently in the group who received diazepam and atropine, although it might be expected to be greater in those who received the narcotic premedication as opiates have been shown to enhance the respiratory depression produced by thiopentone (Eckenhoff and Helrich, 1958) and methohexitone (Dundee, Barron and Nicholl, 1961). A higher incidence of apnoea has also been found to occur after non-narcotic premedication in patients induced with Althesin (Hall, Whitwam and Morgan, 1973). The occurrence of apnoea following etomidate is less than that reported for Althesin (Hall, Whitwam and Morgan, 1973) and for equi-potent doses of thiopentone and methohexitone (Whitwam, 1962). However, the relative potency of etomidate as compared with these agents is not known, so that a strict comparison of the results is not possible.

The higher incidence of apnoea in the patients who received diazepam and atropine was thought to be related to the more frequent appearance of involuntary muscle movements with consequent breath holding in this group. This view might be supported by the fact that in an earlier study (Holdcroft et al., 1976) using the same dose of etomidate and premedicant drugs, the incidence of severe and moderate involuntary muscle movement was considerably less and this was associated with a lower incidence of apnoea.

A significant increase in respiratory rate followed anaesthesia with etomidate in those who received diazepam and atropine, which was not seen following opiate premedication.

The depression of minute volume caused by etomidate was relatively transient and was only significantly lower than control values during the 2nd minute after induction in the patients premedicated with papaveretum and hyoscine. In the dosage used, etomidate would appear to cause less respiratory depression than Althesin, thiopentone and methohexitone, which would suggest that it might be of considerable benefit in obstetric anaesthesia. The major problem with etomidate is the high incidence of involuntary muscle movements during induction, which occasionally resembles convulsive activity. Although the duration of this phenomenon is short and the incidence can be reduced considerably with opiate premedication (Holdcroft et al., 1976), it remains a serious problem which will probably limit the use of the drug.

ACKNOWLEDGEMENTS

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REFERENCES


EFFETS RESPIRATOIRES DE L'ETOMIDATE

RESUME

Les effets respiratoires de l'etomidate, en dose de 0,3 mg/kg ont été étudiés sur des malades pré-traités soit au diazepam et à l'atropine, soit au papaveretum et à l'hyoscine. L'incidence d'apnée a été de 40% sur ceux qui avaient reçu le prétreatment non narcotique et de 27% sur ceux qui avaient reçu le médicament opiacé. Les malades pré-traités au diazepam et à l'atropine ont accusé une augmentation significative de la fréquence respiratoire que l'on a associée à une augmentation significative du débit cardiaque 4 min après le commencement de l'anesthésie. Il ne s'est produit aucune augmentation de ce genre sur ceux qui avaient été pré-traités au papaveretum et à l'hyoscine. Il semblerait que les effets de l'etomidate sur la respiration soient moins prononcés que ceux des autres agents d'induction administrés par voie intraveineuse, mais les mouvements musculaires involontaires pendant l'induction demeurent un problème.
ZUSAMMENFASSUNG

Die Atembeeinflussung von 0,3 mg/kg Etomidat wurde in entweder mit Diazepam und Atropin, oder mit Papaveretum und Hyoszin, vorbehandelten Patienten studiert. In 40% der Patienten, die die nichtnarkotische Vorbehandlung erhielten, trat Atemlähmung ein, verglichen mit 27% der Opiatbehandelten. Diejenigen, die mit Diazepam und Atropin vorbehandelt wurden, wiesen 4 Minuten nach Narkosebeginn eine bedeutsame, mit einer bedeutsamen Minutenvolumsteigerung verbundene Atemfrequenzsteigerung auf. In den mit Papaveretum und Hyoszin Vorbehandelten trat keine derartige Steigerung auf. Es hat den Anschein, dass die Einwirkungen von Etomidat auf den Atem geringer als die anderer intravenöser Einleitungsmitte sind, es bleibt aber die unfreiwillige Muskelbewegung während der Einleitung problematisch.

EFECTOS RESPIRATORIOS DEL ETOMIDATO

Se estudiaron los efectos respiratorios del etomidato (0,3 mg/kg) en pacientes premedicados con, o bien diazepam y atropina, o papaveretum e hioscina. La frecuencia de apnea fue del 40% en los que recibieron la premédicación no narcótica, comparada con el 27% en los que recibieron el opiato. Los premedicados con diazepam y atropina mostraron un aumento significante en la frecuencia respiratoria, que se asoció a un aumento significante en el volumen minuto a los 4 minutos tras la inducción de anestesia. No se produjo semejante aumento en los premedicados con papaveretum e hioscina. Parece que los efectos del etomidato sobre la respiración son menores que los de otros agentes endovenosos de inducción, pero sigue siendo un problema el movimiento muscular involuntario durante la inducción.