VENTILATION, VENTILATORY CARBON DIOXIDE AND HORMONAL RESPONSE DURING HALOTHANE ANAESTHESIA AND SURGERY IN CHILDREN AFTER MIDAZOLAM PREMEDICATION

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Although diazepam has suitable anxiolytic and amnesic properties, its use as a premedicant has been limited by local irritation when given i.m. (Siebke, Ellertsen and Lind, 1976), and its unpredictable bioavailability (Morselli et al., 1973; Dundee, Gamble and Assaf, 1974; Korttila and Linnoila, 1975). Midazolam, which is water soluble, has almost no local irritating effect (Cole, 1982; Vinik, Reves and Wright, 1982) and is absorbed rapidly after i.m. administration (Creviöier et al., 1981). It has potent anxiolytic (Dundee et al., 1980) and amnesic effects (Dundee and Wilson, 1980) and has been used i.m. in adults as a premedicant in doses of 0.07 and 0.08 mg kg\(^{-1}\) (Vinik, Reves and Wright, 1982; Fragan et al., 1983).

In the present study the influence of two doses of midazolam (0.1 and 0.2 mg kg\(^{-1}\)) i.m. for premedication, on ventilation, ventilatory response to carbon dioxide and hormonal stress response was studied in connection with minor surgical procedures during halothane anaesthesia. The concentrations of catecholamines, ACTH and cortisol were measured immediately after induction, during undisturbed anaesthesia, during surgery and 15 min after the end of the surgical procedure. Sedation was better and plasma catecholamine concentrations during undisturbed anaesthesia were less in children receiving the larger dose of midazolam. During surgery and in recovery there were no differences in hormone concentrations. In recovery, the concentrations of all hormones were significantly greater compared with during undisturbed anaesthesia. During surgery, \(VE\) and respiratory rate were somewhat lower in group \(M_{0.2}\) while \(E^*_{CO_2}\) was similar. A dose dependent depression of the response to carbon dioxide was found. However, clinically, the ventilatory response to carbon dioxide after surgery was considered to be adequate in both groups.

SUMMARY

In 14 intubated, spontaneously breathing children with body weight (bw) ranging from 8.3 to 25.6 kg, the influence of midazolam 0.1 mg kg\(^{-1}\) i.m. (group \(M_{0.1}\), \(n = 7\)) and 0.2 mg kg\(^{-1}\) i.m. (group \(M_{0.2}\), \(n = 7\)) as premedication, on sedation, ventilation, ventilatory response to carbon dioxide and hormonal stress response was studied in connection with minor surgical procedures during halothane anaesthesia. The concentrations of catecholamines, ACTH and cortisol were measured immediately after induction, during undisturbed anaesthesia, during surgery and 15 min after the end of the surgical procedure. Sedation was better and plasma catecholamine concentrations during undisturbed anaesthesia were less in children receiving the larger dose of midazolam. During surgery and in recovery there were no differences in hormone concentrations. In recovery, the concentrations of all hormones were significantly greater compared with during undisturbed anaesthesia. During surgery, \(VE\) and respiratory rate were somewhat lower in group \(M_{0.2}\) while \(E^*_{CO_2}\) was similar. A dose dependent depression of the response to carbon dioxide was found. However, clinically, the ventilatory response to carbon dioxide after surgery was considered to be adequate in both groups.

PATIENTS AND METHODS

Anaesthetic technique

Fourteen children (ASA class I) were studied in groups premedicated with atropine 0.02 mg kg\(^{-1}\)
and either midazolam 0.1 mg kg\(^{-1}\) (group M\(_{0.1}\)) or midazolam 0.2 mg kg\(^{-1}\) i.m. (group M\(_{0.2}\)). Minute ventilation \((V_E)\), tidal volume \((V_T)\), respiratory frequency \((f)\) and end-tidal carbon dioxide concentration \((E_{CO_2})\) were measured before and during surgery and immediately after surgery with and without the inhalation of carbon dioxide. Blood for analysis of hormone concentrations was drawn after the induction of anaesthesia, during surgery and 15 min after the end of surgery. The study was approved by the Ethics Committee at the hospital. Characteristics of the patients and details of the surgical procedures are presented in table I.

After the induction of anaesthesia with cyclopropane in oxygen \((F_{O_2} 0.5)\), suxamethonium 1–1.5 mg kg\(^{-1}\) was used to facilitate intubation. The patients were then allowed to resume spontaneous breathing with nitrous oxide in oxygen \((F_{O_2} 0.5)\), and 0.5–2.0\% halothane. A modified T-piece (Mapleson F system) (fig. 1) was used and fresh gas flows were adjusted to prevent rebreathing. Arterial pressure and heart rate were measured automatically (Dinamap 850: Applied Medical Research, Tampa, Florida, U.S.A.). The paediatric airway adaptor of an in-line capnograph (Hewlett-Packard 14360 A) and a heated pneumotachograph (Fleisch No. 0) with a differential pressure manometer (Validyne MP 45-1-871, range ±2 cm H\(_2\)O) were placed in the patient limb of the T-piece for measurements of \(E_{CO_2}\) and \(V_E\) (fig. 1). \(V_T\) was measured by

![Reservoir bag CO2 Patient CO2 FGF](https://academic.oup.com/bja/article-lookup/doi/10.1093/bja/58.11.1234)

**Fig. 1.** Schematic presentation of the breathing system. \(CO_2\) = position of in-line capnograph; \(\dot{V}\) = position of pneumotachograph; FGF = fresh gas flow inlet.

### Table I. Mean values (+/− SD) for body weight, premedication time and duration of operation are presented in the two groups.

*Year, months, weeks*

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age*</th>
<th>Body weight (kg)</th>
<th>Diagnosis</th>
<th>Premed. time (min)</th>
<th>Operation time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3, 8, 0</td>
<td>16.9</td>
<td>Squint</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>3, 5, 0</td>
<td>15.0</td>
<td>Extirp. of neck lymph node</td>
<td>61</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>6, 2, 0</td>
<td>25.6</td>
<td>Extirp. of thyroglossal cyst</td>
<td>80</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>6, 0, 0</td>
<td>22.5</td>
<td>Undescended testicle</td>
<td>70</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>2, 11, 1</td>
<td>13.0</td>
<td>Squint</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>7, 8, 0</td>
<td>19.5</td>
<td>Exploration left groin</td>
<td>75</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>4, 9, 0</td>
<td>18.0</td>
<td>Undescended testicle</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>Mean ± 1SD</td>
<td>18.5 ± 4.1</td>
<td></td>
<td></td>
<td>73.4 ± 17.9</td>
<td>47.7 ± 20.9</td>
</tr>
</tbody>
</table>

Midazolam 0.02 mg kg\(^{-1}\) + atropine 0.02 mg kg\(^{-1}\)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age*</th>
<th>Body weight (kg)</th>
<th>Diagnosis</th>
<th>Premed. time (min)</th>
<th>Operation time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8, 4, 3</td>
<td>20.0</td>
<td>Excision of submand. gland.</td>
<td>75</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>2, 7, 1</td>
<td>16.3</td>
<td>Inguinal hernia</td>
<td>45</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>8, 5, 2</td>
<td>23.6</td>
<td>Sympyseal web</td>
<td>50</td>
<td>102</td>
</tr>
<tr>
<td>4</td>
<td>1, 5, 0</td>
<td>8.3</td>
<td>Extirp. of neck lymph node</td>
<td>75</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>4, 8, 0</td>
<td>15.0</td>
<td>Osteoid osteoma left leg</td>
<td>70</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>8, 4, 2</td>
<td>25.0</td>
<td>Squint</td>
<td>40</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>7, 8, 2</td>
<td>24.2</td>
<td>Retinoblastoma</td>
<td>50</td>
<td>55</td>
</tr>
<tr>
<td>Mean ± 1SD</td>
<td>18.9 ± 5.6</td>
<td></td>
<td></td>
<td>57.9 ± 13.9</td>
<td>76.7 ± 24.3</td>
</tr>
</tbody>
</table>

1235
electrical integration of the flow signal. Flow, volume and carbon dioxide signals were recorded on a u.v. recorder (S.E. Labs (EMI) Ltd, S.E. 3006). Certified gases were used to calibrate the capnograph and a 50-ml syringe containing 50% nitrous oxide in oxygen mixture to calibrate the volume.

The resistance of the system was 10.0 cm H₂O litre⁻¹ s⁻¹ up to flow rates of 10 litre min⁻¹ and its deadspace was 6 ml (measured by water displacement).

**Biochemistry**

Samples for the analysis of ACTH and cortisol concentrations were collected in test tubes containing EDTA 10.0 mg/7 ml blood and aprotinin (Trasylol, Bayer, Wester Germany) 300 KIE/7 ml blood which had been prechilled in ice-water. The samples were kept at 0 °C until centrifugation in a refrigerated centrifuge. The plasma was then stored at −70 °C. ACTH was determined by radioimmunooassay (ACTHK, Sorin Biomedica, Italy) using rabbit antiserum raised against porcine ACTH coupled to bovine serum albumin. Human ACTH was used as standard and [³²⁵I]-ACTH as tracer (Hedner, Nordén and Valdemarsson, 1981). The concentration of cortisol was determined using solid phase radioimmunoassay (Gammacoat, Clinical Assays, Mass. U.S.A.) with rabbit anti-cortisol serum attached to test tubes as binding protein and [³²⁵I]-cortisol as tracer. Samples to permit measurement of the total catecholamine concentration were drawn in tubes with 20 μl of anticoagulant and anti-oxidant (EGTA 90 mg ml⁻¹, glutathione 60 mg ml⁻¹ and pH 6.0-7.4) per ml of blood. A modification of the radioenzymatic method of Passon and Peuler (1973) (Upjohn Diagnosis, U.S.A.) based on rat liver catechol-O-methyltransferase and S-adenosyl-L-methionine-[³H-methyl] was used. After periodate oxidation, the resulting [³H]-vanillin was extracted and measured by liquid scintillation. Between-runs coefficient of variation for the assay is 4-10% depending on concentration. Normal values for adults are 0.8-2.4 nmol litre⁻¹.

**Measurements**

The sedative effect of the premedication was evaluated, according to the scoring system given in table II, by the anaesthetist in charge of the patient. He was not involved in the study and did not know the premedication used. Because of diurnal variations in the hormone concentrations, blood samples were drawn between 10 a.m. and 2 p.m. Immediately after induction and during undisturbed anaesthesia before tracheal intubation (UA), blood was drawn from a peripheral vein. The second blood sample was drawn during surgery (DS) and the third, 15 min (P) into the postoperative period.

At least 20 min after the induction of anaesthesia but before the start of surgery (PS), $\dot{V}E$, $\dot{V}T$, $f$, $\text{E}'_{\text{CO}_2}$, arterial pressure and heart rate were measured, and repeated at a stable state during surgery (DS) and immediately after surgery during continued anaesthesia before extubation, with and without the addition of about 2% carbon dioxide to the inspired gas.

**Statistics**

Mean values, standard deviation (SD) and standard error of the mean (SEM) were calculated and unpaired Student's t test applied to mean data.

**RESULTS**

In group $M_{0.1}$, premedication was given 73±18 min (mean±1 SD) and in group $M_{0.5}$ 58±14 min (mean±1 SD) before the induction of anaesthesia (ns) (table I). Evaluation of preoperative sedation resulted in a mean scoring of 4.7 after $M_{0.1}$ and 5.7 after $M_{0.5}$. In the anaesthetic room immediately after induction, respiratory rate and heart rate (mean values±1 SD) were 35±11 b.p.m. and 108±23 beat min⁻¹ with the smaller and 32±7 b.p.m. and 109±9 beat min⁻¹ with the larger dose of midazolam. $\text{E}'_{\text{CO}_2}$ (mean±1 SD) was 4.9±0.6% with $M_{0.1}$ and 5.3±0.8% with $M_{0.5}$. None of these differences was statistically significant. At measurements before, during and after surgery with and without carbon dioxide...
inhalation, systolic arterial pressure and heart rate were similar within each group as well as between the two groups (table III).

**Ventilation**

In the group of children receiving the smaller dose of midazolam, \( \dot{V}_E \) was greater during surgery because of more rapid respiratory rates. \( \dot{E}'_{CO_2} \) was similar in the two groups (fig. 2). After surgery, \( \dot{E}'_{CO_2} \) was unaltered before and during the inhalation of 2.13 ± 0.22% (mean ± 1 SD) carbon dioxide in the \( M_{0.1} \) group. In group \( M_{0.2} \), \( \dot{E}'_{CO_2} \) increased by about 8% (ns) when 2.18 ± 0.29% (mean ± 1 SD) carbon dioxide was inhaled after surgery. At comparisons before and during the inhalation of carbon dioxide, \( \dot{V}_E \) and \( VT \) were both increased to the same extent in the two groups (fig. 3). The relationship between percentage difference in \( \dot{V}_E \) and the change in \( \dot{E}'_{CO_2} \) revealed a somewhat more depressed ventilation in group \( M_{0.1} \) compared with that in group \( M_{0.1} \) (fig. 4).

**Stress response**

Plasma catecholamine concentration (mean ± 1 SD) was 4.40 ± 1.82 nmol litre\(^{-1}\) in \( M_{0.1} \) during undisturbed anaesthesia after the induction of anaesthesia (\( P < 0.05 \)) (fig. 5). There were no

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**Table III. Mean values (± 1 SD) of systolic arterial pressure (SAP) and heart rate (HR) in the two groups \( M_{0.1} \) and \( M_{0.1} \) before, during and after surgery without and with carbon dioxide breathing**

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>During surgery</th>
<th>After surgery</th>
<th>After surgery during CO(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( M_{0.1} )</td>
<td>103 ± 7.3</td>
<td>104 ± 4.5</td>
<td>106 ± 4.9</td>
<td>108 ± 7.9</td>
</tr>
<tr>
<td>( M_{0.1} )</td>
<td>98 ± 6.7</td>
<td>100 ± 8.2</td>
<td>101 ± 7.6</td>
<td>103 ± 9.4</td>
</tr>
<tr>
<td><strong>HR (beat min(^{-1}))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( M_{0.1} )</td>
<td>112 ± 24</td>
<td>120 ± 24</td>
<td>124 ± 20</td>
<td>127 ± 18</td>
</tr>
<tr>
<td>( M_{0.1} )</td>
<td>112 ± 12</td>
<td>117 ± 12</td>
<td>115 ± 13</td>
<td>119 ± 13</td>
</tr>
</tbody>
</table>

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\( \dot{V}_E \) (ml/min\(^{1}\))

\( VT \) (ml)

\( f \) (b.p.m.)

\( \dot{E}'_{CO_2} \) (%)

**Fig. 2.** Mean values ± SEM of minute ventilation (\( \dot{V}_E \)), tidal volume (\( VT \)), respiratory rate (\( f \)) and end-tidal carbon dioxide concentration (\( \dot{E}'_{CO_2} \)) before surgery (PS) and during surgery (DS) after premedication with midazolam 0.1 mg kg\(^{-1}\) (○—○) and with midazolam 0.2 mg kg\(^{-1}\) (●—●).
differences in plasma catecholamines between the two groups during surgery, and 15 min after the end of the operation.

In group $M_{0.13}$, plasma catecholamine concentration during undisturbed anaesthesia was not further increased during surgery, whereas the mean value during undisturbed anaesthesia in group $M_{0.1}$ was increased by 255% during surgery ($P < 0.05$). In both groups, mean concentrations of the catecholamines were significantly increased 15 min after surgery ($P < 0.05$) (fig. 5). During undisturbed anaesthesia, the mean ($\pm 1$
MIDAZOLAM PREMEDICATION IN CHILDREN

400
T
1000

1239

FIG. 6. Mean values (± SEM) of plasma ACTH concentration at UA, DS and P in group M0.1 (O—O) and in group M0.3 (●—●) *P < 0.05; **P < 0.01; for the differences within each group compared with UA.

300-
W
200
100-

UA
DS
P

FIG. 7. Mean values (± SEM) of plasma cortisol concentration at UA, DS and P in group M0.1 (O—O) and in group M0.3 (●—●) *P < 0.05; **P < 0.01; ***P < 0.001 for the differences within each group compared with UA.

SD) plasma ACTH concentrations were similar in the two groups. There were no significant differences in ACTH concentration between the two groups, although the mean values during and after surgery were somewhat greater in group M0.1 than in group M0.3 (fig. 6). In both groups, mean plasma concentrations of ACTH had increased significantly during and after surgery when compared with values during undisturbed anaesthesia (P < 0.05; P < 0.01) (fig. 6).

Plasma cortisol concentration (mean ± 1 SD) was similar in the two groups (fig. 7); in both, plasma cortisol concentration had increased during and 15 min after surgery when compared with the values obtained during undisturbed anaesthesia (P < 0.05; P < 0.01; P < 0.001).

DISCUSSION

Body weight and type of surgery performed were comparable in the two groups of children. Atropine was used as an anticholinergic since central sedative and amnesic effects are less with atropine than with hyoscine. The mean premedication time was about 15 min longer in group M0.1 than in group M0.3. This could mean that the peak effect of midazolam in group M0.1 was over before the children arrived in the anaesthetic room and this could have had some influence on the sedative scoring. However, Vinik, Reves and Wright (1982) found that sedation was better at 60 min than at 45 min after the i.m. administration of midazolam. Fragen and colleagues (1983) also found that the decrease in anxiety was better at 90 min than at 60 min after the i.m. injection of midazolam. Thus the difference in the premedication times in the present study was not thought to affect significantly the evaluations of sedation and stress response.

In the group of children receiving the higher dose of midazolam, sedative scores were better than in the children receiving the smaller dose. This showed, as has been demonstrated previously for diazepam (Brown and Dundee, 1968), that the sedative and anxiolytic effects of midazolam are dose dependent. Side effects of anxiolytic drugs
also increase with greater dose and it is known that diazepam depresses the central regulation of respiration—decreasing the carbon dioxide response (Catchlove and Kafer, 1971; Jordan, Lehane and Jones, 1980) and inspiratory drive (Clerque et al., 1981). Although studies similar to those cited for diazepam have not yet been undertaken with midazolam, the close chemical relationship between the various benzodiazepines and, in particular, between diazepam and midazolam (Reves, Corssen and Holcomb, 1978) suggests that the same neuropharmacological mechanisms would be involved in their actions. That is, one would expect midazolam to depress respiration in a dose-dependent manner.

However, end-tidal carbon dioxide concentrations measured in the anaesthetic room immediately after induction of sleep were similar in the two groups. This did not suggest a more profound respiratory depressant effect of midazolam 0.2 mg kg⁻¹, although sedative scores were higher and plasma catecholamine concentrations lower during undisturbed anaesthesia when the higher doses were used. Furthermore, the respiratory pattern before and during surgery was characterized by a somewhat lower minute ventilation and respiratory rate in group M₁, while $V'_\text{CO}_2$ was unchanged between the two groups (fig. 2). This indicated a more favourable respiratory pattern with the higher dose, since lower respiratory rates are known to reduce wasted ventilation under similar conditions (Rose and Froese, 1980; Lindahl, Hulse and Hatch, 1984). Moreover, both groups in this study responded adequately to the inhalation of carbon dioxide just before the recovery period (2 h after administration of midazolam). Minute ventilation and tidal volume increased equally and respiratory rates were virtually unchanged—demonstrating a similar responsiveness to carbon dioxide in both groups.

The relationship between changes in $V'_E$ and $V'_\text{CO}_2$ (fig. 4) revealed, in some of the children receiving the higher dose of midazolam, a slightly reduced ventilatory response to carbon dioxide. Thus, theoretically, a dose-dependent depression of the response to carbon dioxide similar to that found previously for diazepam (Catchlove and Kafer, 1971; Jordan, Lehane and Jones, 1980; Clerque et al., 1981) might exist. However, the number of patients in this study (which was designed primarily to evaluate the effects of the premedication) was too small to demonstrate conclusively the dose-dependent effect of midazol-


