INFUSION OF MIDAZOLAM IN PAEDIATRIC PATIENTS AFTER CARDIAC SURGERY

A. R. LLOYD-THOMAS AND P. D. BOOKER

Critically ill patients who require intensive care are often in pain, fearful and anxious. Although analgesics can provide pain relief, and reassurance and communication can do much to relieve anxiety (Henschel, 1977; Shovelton, 1979), sedation is required frequently (Farina, Levati and Tognoni, 1981)—not only to provide anxiolysis, but also in the control of physically undesirable factors such as increases in intracranial pressure (Willatts, 1985). Clinicians have recently lost two useful hypnotic agents: Althesin (alphaxalone-alphadolone, Glaxo) was withdrawn by the manufacturers and etomidate (Hypnomidate, Jannsen) was shown to impair adrenocortical function when given by infusion over prolonged periods of time (Ledingham and Watt, 1983; Wagner et al., 1984).

With a more limited range of hypnotic agents available, a popular combination is that of an opioid and a benzodiazepine (Campos, Herraez and Marcos, 1980; Merriman, 1980; Miller-Jones and Williams, 1980; Farina, Levati and Tognoni, 1981; Reves, 1984). Diazepam has been used widely (Merriman, 1980), but the long elimination half-life and hypnotically active metabolite (n-desmethyldiazepam) may prolong recovery (Reves, 1984; Willatts, 1985).

Unlike diazepam, midazolam is water soluble and non-irritant to peripheral veins (Dundee et al., 1980; Kawar and Dundee, 1982). Its elimination half-life is 10 times less, and its total body clearance is some 20 times greater, than that of diazepam (Reves, 1984). The principal metabolite of midazolam is α-hydroxymidazolam, which is both hypnotically less active and has a shorter elimination half-life than the parent compound.

SUMMARY

Midazolam was given, by infusion, for the sedation of 10 children receiving intensive care after cardiac surgery. Plasma concentrations greater than 250 ng ml⁻¹ were required for adequate sedation. Midazolam did not cumulate in eight of the 10 children, and these patients excreted the drug in a fashion similar to that by adults. However, midazolam did accumulate in two children, one with profound hepatic disturbance. In one of these patients recovery was slow following cessation of the infusion.

Thus, when compared with diazepam, midazolam would be expected to have a shorter duration of action and, hence, be potentially a more useful agent with which to provide sedation i.v.

However, significant delays in awakening have been reported in some patients following sedation with midazolam (intermittent bolus and infusion) (Byatt, 1984; Byrne, Yeoman and Mace, 1984). In this unit, midazolam has been used widely in children requiring sedation following cardiac surgery (Booker, Beechey and Lloyd-Thomas, 1986). As a continuation of this study, the pharmacodynamics of midazolam when given by infusion have been investigated.

PATIENTS AND METHODS

The study was approved by the Hospital Ethical Committee and informed parental consent was obtained.

Selection of patients

Ten patients (two female) undergoing elective cardiac surgery requiring cardiopulmonary bypass were studied. Their ages ranged from 6 months to 8.75 yr. The defects requiring surgery are listed in table I. Patients who had received benzodiazepines in the preceding 2 weeks or who...
had clinical and biochemical evidence of hepatic dysfunction were excluded.

Anaesthesia

Patients older than 12 months of age received trimiprazine tartrate 1.5 mg kg⁻¹ by mouth and morphine 0.25 mg kg⁻¹ plus atropine 20 μg kg⁻¹ i.m. given, respectively, 3 h and 1 h before surgery.

Anaesthesia was induced with thiopentone 4 mg kg⁻¹ and morphine 0.25 mg kg⁻¹ i.v. The trachea was intubated, following the administration of vecuronium 0.15 mg kg⁻¹, and anaesthesia maintained with 50% nitrous oxide in oxygen. Incremental doses of vecuronium 0.05 mg kg⁻¹ were given as required, the last dose being administered just after the discontinuation of cardiopulmonary bypass. All patients were ventilated by hand, using the Jackson–Rees modification of Ayre’s T piece, with sufficient gas flow to produce mild hypocarbia (PaCO₂ 4.3–4.9 kPa).

Once appropriate monitoring had been established, a bolus of midazolam 0.2 mg kg⁻¹ i.v. was given, and an infusion commenced at 2 μg kg⁻¹ min⁻¹. This infusion was maintained throughout the operation and discontinued only at the time of the last skin suture. A dedicated peripheral line was used for the administration of midazolam.

Cardiopulmonary bypass

Core cooling to 16–26 °C was used in all patients. Re-warming to nasopharyngeal temperatures greater than 35 °C was achieved before the discontinuation of the bypass.

Sedation in the Intensive Care Unit

On arrival in the intensive care unit, and every 15 min thereafter, a standard stimulus (an orange stick drawn firmly along the sole of the foot) was applied. When the children had recovered sufficiently to respond by withdrawal of the leg, or to show spontaneous eye opening, they were re-sedated. A second bolus of midazolam 0.2 mg kg⁻¹ i.v. was given and the infusion re-started at 2 μg kg⁻¹ min⁻¹. An infusion of morphine was commenced at 0.33 μg kg⁻¹ min⁻¹, a dose shown to produce satisfactory analgesia in children (Lynn, Opheim and Tyler, 1984). Vecuronium could be given if required, with the dose strictly limited to a maximum of 0.04 mg kg⁻¹ h⁻¹.

The level of sedation was assessed by the nursing staff and the authors. Sedation was considered to be adequate when the children were asleep, tolerating artificial ventilation and yet able to respond slightly to nursing procedures such as endotracheal suction. If the patient was restless, the rate of infusion was increased in steps of 1 μg kg⁻¹ min⁻¹, every 30 min until satisfactory sedation was achieved. If no response was elicited the rate of infusion was decreased.

Artificial ventilation

During intermittent positive pressure ventilation (IPPV) the PₐCO₂ was maintained in the range of 4.3–4.9 kPa. The duration of IPPV was determined by cardiovascular and respiratory variables. When these had improved such that weaning from IPPV was appropriate the morphine infusion was stopped. During intermittent mandatory ventilation (IMV) and spontaneous respiration with continuous positive airway pressure (CPAP), patients were sedated with midazolam alone. When the children were considered fit for extubation the midazolam infusion was stopped. Only when the patients were able to respond to

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (months)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Defect requiring surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>M</td>
<td>8.23</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>M</td>
<td>6.15</td>
<td>Transposition of the great arteries</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>M</td>
<td>7.7</td>
<td>Transposition of the great arteries</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>M</td>
<td>16.6</td>
<td>Closure of ventricular septal defect</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>M</td>
<td>17.2</td>
<td>Mixed mitral valve disease</td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>M</td>
<td>23</td>
<td>Closure of ventricular septal defect</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>F</td>
<td>14</td>
<td>Closure of ventricular septal defect</td>
</tr>
<tr>
<td>8</td>
<td>105</td>
<td>M</td>
<td>21.6</td>
<td>Atrio-ventricular canal defect</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>F</td>
<td>9</td>
<td>Closure of ventricular septal defect</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>M</td>
<td>6.4</td>
<td>Debanding of pulmonary artery and closure of ventricular septal defect</td>
</tr>
</tbody>
</table>
verbal commands or were opening their eyes spontaneously was extubation performed.

While the patient was on full ventilation, the arterial and central venous pressures were monitored continuously. In addition, during spontaneous breathing, the tidal volume, minute volume, respiratory rate and $P_{a}CO_{2}$ were measured. The urine output was recorded hourly.

**Measurement of midazolam concentration**

Blood samples for the assay of midazolam concentration were obtained at the following times:

1. Base-line after induction.
2. At the last skin suture.
3. On awakening on the ICU.
4. At 21.00 h and 09.00 h daily.
5. On cessation of the midazolam infusion.
6. On extubation.
7. When possible during recovery.

Immediately following sampling, plasma was separated and frozen. Analysis was performed by the gas—liquid chromatography method of Heizmann and von Alten (1981) with electron capture detection.

Only limited patient sampling was possible once the children had awoken. Following cessation of the infusion, three samples were collected from five patients. From these three data points, in each patient, the approximate elimination half-life was calculated by least squares regression analysis of log drug concentrations against time.

**RESULTS**

Satisfactory sedation was achieved in all patients. In eight children the mean duration of infusion was 23.4 h (SEM 0.69 h). Two patients received longer infusions (table II), they also handled the drug abnormally and their results are presented later.

In the eight patients the mean duration of the perioperative infusion was 204 min (SEM 17), after which the mean plasma concentration of midazolam was 257 ng ml$^{-1}$ (SEM 29.3). The mean time to awakening on the ICU following surgery was 114 min (SEM 12.5) during which the mean plasma midazolam concentration had decreased to 140.5 ng ml$^{-1}$ (SEM 21.7) (table III, fig. 1).

After stable clinical sedation had been achieved with both midazolam and morphine, the mean plasma concentration of midazolam was 421 ng mg$^{-1}$ (SEM 95.6). The mean infusion rate

### Table II. Duration of the midazolam infusions

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Duration of infusion (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>23.5</td>
</tr>
<tr>
<td>4</td>
<td>26.25</td>
</tr>
<tr>
<td>5</td>
<td>68.5</td>
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<td>6</td>
<td>113.5</td>
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<td>7</td>
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<td>8</td>
<td>25.5</td>
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<tr>
<td>9</td>
<td>21.5</td>
</tr>
<tr>
<td>10</td>
<td>22.45</td>
</tr>
</tbody>
</table>

### Table III. Duration and plasma concentration achieved at similar stages during the infusion of midazolam in eight children. Mean (± SEM). *$n = 7$

<table>
<thead>
<tr>
<th>Period</th>
<th>Duration (min)</th>
<th>Plasma midazolam concentration (ng ml$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative infusion*</td>
<td>204</td>
<td>257 (29.3)</td>
</tr>
<tr>
<td>Time to awakening after surgery</td>
<td>114</td>
<td>140 (21.7)</td>
</tr>
<tr>
<td>Duration of sedation with midazolam and morphine</td>
<td>1033</td>
<td>421 (95.6)</td>
</tr>
<tr>
<td>Duration of sedation with midazolam alone</td>
<td>246</td>
<td>530 (74.5)</td>
</tr>
<tr>
<td>Time to awakening and extubation in ICU</td>
<td>109</td>
<td>254 (51)</td>
</tr>
</tbody>
</table>

**Fig. 1.** Mean plasma concentrations of midazolam in eight patients at the following times: 1, at the last skin suture; 2, postoperative awakening in the ICU; 3, at steady clinical sedation the following day; 4, whilst sedated by midazolam alone and breathing on CPAP; 5, on awakening before extubation. Bars indicate ± SEM, *$n = 7$. 

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for the whole period of sedation was 3.1 μg kg⁻¹ min⁻¹ (SEM 0.3), with a range of 2.5 μg kg⁻¹ min⁻¹. While the patients were being sedated with midazolam and morphine, the mean midazolam infusion rate was 2.88 μg kg⁻¹ min⁻¹ (SEM 0.3). However, when the patients were breathing spontaneously on CPAP, with midazolam as the only sedative drug, a significantly higher mean infusion rate (4.06 μg kg⁻¹ min⁻¹ (SEM 0.3)) was required to maintain the same clinical level of sedation (0.01 < P > 0.001). During sedation with midazolam alone the mean plasma concentration increased to 530 ng ml⁻¹ (SEM 74.5). Plasma concentrations correlated closely with the mean infusion rate (r = 0.87, 0.05 < P < 0.02).

In the eight children the cardiovascular variables remained stable, during the administration of the bolus doses as well as the infusions of midazolam. During spontaneous respiration on CPAP the PaCO₂, minute volume, tidal volume and respiratory rate were within normal and expected values.

Following the discontinuation of the infusion of midazolam in the intensive care unit, the mean time to achieve a clinical state which would allow extubation was 109 min (SEM 12.1), during which the plasma concentration decreased to a mean of 254 ng ml⁻¹ (SEM 51). However, there was no correlation between the plasma concentration when the infusion was stopped and the time taken to recover (r = —0.25). There was no correlation between the plasma concentrations on awakening after surgery and those measured in relation to the second awakening (before extubation) (r = 0.348). In general, however, on both occasions, plasma concentrations on awakening were approximately one-half of those measured when the infusion was stopped (table IV).

From subsequent sampling it was possible to calculate the approximate elimination half-life in five patients. The mean elimination half-life was 4 h (range 2–8). Throughout the period of sedation the mean concentration of the metabolite alpha hydroxymidazolam was 26% (SEM 5%) of the mean midazolam concentration.

Much higher plasma concentrations were recorded in two children. In one (No. 6), hepatic impairment and renal failure occurred. In this child the mean rate of infusion (3.17 μg kg⁻¹ min⁻¹) was not significantly higher than that in the other children. The increase in plasma concentration corresponded with increases in plasma liver enzyme and bilirubin concentrations (fig. 2). The

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Plasma concentration (ng ml⁻¹)</th>
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<tbody>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>1</td>
<td>117</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>114</td>
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<tr>
<td>9</td>
<td>122</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
</tr>
</tbody>
</table>

Fig. 2. Plasma concentrations of midazolam, 1-hydroxymidazolam, total bilirubin, aspartate transaminase and alanine transaminase as related to infusion rate in patient No. 6.
MIDAZOLAM INFUSIONS IN CHILDREN

1113

FIG. 3. Plasma concentrations of midazolam and 1-hydroxy-
midazolam as related to infusion rate in patient No. 5.

ratio of plasma α-hydroxymidazolam to midazolam was only 7.5% in this child, as compared with a mean of 26% in the other patients. Recovery was slow, following cessation of the midazolam infusion, taking 20 h and 30 min. The plasma concentration on awakening exceeded 1200 ng ml⁻¹ (table IV, fig. 2). The second patient (No. 5) whose mean infusion rate (3.73 μg kg⁻¹ min⁻¹) was also not significantly higher than the other children also had high plasma concentrations (fig. 3). The ratio, α-
hydroxymidazolam to midazolam, of 17% was also reduced in comparison with the other patients. Recovery (200 min) was significantly longer than that of the other patients (0.05 < P > 0.1) and the plasma concentration of midazolam on awakening was 3315 ng ml⁻¹.

DISCUSSION

Reliable sedation with minimal side effects, and a rapid excretion which is independent of the body’s metabolic pathways, is a goal unattained by any currently available drug.

In this investigation, reliable sedation was achieved in all patients with the infusion of morphine and midazolam. Periods of wakefulness, which are possible when hypnotic agents are prescribed on an “as required” basis (Miller-Jones and Williams, 1980) were avoided. During spontaneous respiration with CPAP, midazolam was the sole sedative agent and significantly higher infusion rates were required by all the children to achieve clinically equivalent sedation.

This confirms the useful synergistic properties of morphine and midazolam.

Respiratory depression (depression of both the ventilatory response to carbon dioxide and the mouth occlusion pressure to carbon dioxide) of demonstrable CNS origin, has been described in patients given bolus doses of midazolam (Forster et al., 1980). However during weaning from IPPV none of the children showed any clinical evidence of respiratory depression. It has been suggested that “tolerance” to the respiratory depressant effects of midazolam occurs with repeated bolus dosage (Al-Khudhairi, Askitopoulou and Whitwam, 1982), a feature which could also occur in association with an infusion of the drug.

A reasonably good association has been reported between measured plasma midazolam concentrations, psychological performance and subjective sedation (Kanto and Allonen, 1982; Crevosier et al., 1983). Following a single i.v. dose of midazolam in adult volunteers under laboratory conditions, at concentrations of greater than 300 ng ml⁻¹ the subjects were unrousable (Alloen, Zeigler and Klotz, 1981; Crevoisier et al., 1983). When combined with morphine the mean plasma concentration of midazolam, at steady clinical sedation in the children studied, was 421 ng ml⁻¹. This increased to 530 ng ml⁻¹ during sedation with midazolam alone, when a higher rate of infusion was required. At these values the children were just slightly responsive to nursing procedures, yet able to tolerate IPPV. The range of plasma concentrations required to achieve clinically equivalent sedation in all the children studied was wide, but no child was adequately sedated with a plasma midazolam concentration of less than 250 ng ml⁻¹. Variability in the subjective assessment of the degree of sedation by the nursing staff could possibly have contributed to this wide range. However, only six out of a total of 30 alterations in the rate of infusion were made in the absence of an independent assessment by the authors, thus minimizing observer variation.

Within 165 min of stopping the infusion, eight children had recovered sufficiently to permit extubation of the trachea. The time to awakening following cessation of prolonged sedation was similar to that taken to awake following the shorter infusion during the perioperative period (table IV). In general, the plasma midazolam concentrations present at both times of awakening were approximately one-half those present when the infusion was stopped. However, in all but two
children the plasma midazolam concentration on awakening before extubation was at least twice that present on awakening following surgery (table IV). The mean concentration on awakening before extubation was 254 ng ml⁻¹, which might be expected to cause marked sedation. Considerable cerebral tolerance to the depressant effects of the other benzodiazepines has been reported although, more usually, after several days' administration (Greenblatt and Shader, 1978; Dundee, 1979). The rapid development of cerebral "tolerance" could not account for these findings in our patients.

Prediction of the time to recovery after cessation of the infusion of midazolam was not possible from either the plasma drug concentrations or their half-lives. While in single-dose studies in healthy volunteers correlation between plasma concentration and clinical effect is reliable it appears, from this series, that this correlation is lost. Measured plasma concentrations of midazolam appeared to follow the trend of sedation in these children, but not in any precise manner.

Lack of cumulation with intermittent bolus administration has been reported in a group of adult patients following cardiac surgery (Lowry et al., 1985). If the clearance values in paediatric patients were similar to those previously measured in adults (Klotz and Reimann, 1984), plasma concentrations of between 200 and 850 ng ml⁻¹ would be expected from the infusion rates used in these children. Eight of the 10 children fell within this range, thus implying a similar rate of clearance of midazolam. Midazolam accumulated in only two children.

The elimination half-life of midazolam in young healthy humans of normal body habitus is 1–4 h (Greenblatt et al., 1984). Of the five children in whom approximate elimination half-lives could be calculated, three were within the same range as the adults, while two were slightly prolonged at 6.5 and 8 h. In neither of the latter children was recovery prolonged.

The principal metabolite of midazolam is \( \alpha \)-hydroxymidazolam (Reves et al., 1985). In this series the ratio of drug to metabolite (26%) was similar to that found in healthy adult volunteers (Vree, 1982). This provides further evidence that these children handled midazolam in a normal fashion.

However, in two children midazolam appeared to accumulate. In the first patient a poor cardiac output following surgery with associated splanchnic hypoperfusion was responsible for both the hepatic and renal injury. As a result the hepatic metabolism of midazolam was impaired and accumulation occurred (fig. 3). A low ratio of \( \alpha \)-hydroxymidazolam to midazolam (7.5%) supports the impression of failure of metabolism. Recovery following cessation of the midazolam infusion was slow. In the second child there was no clinical or laboratory evidence of hepatic disturbance, yet midazolam appeared to accumulate. His recovery, although significantly longer than the other children, was not unacceptably prolonged.

Both of these children showed considerable "tolerance" to the sedative effect of midazolam, in that they awoke, after prolonged sedation, at considerably higher plasma concentrations than on their initial admission to the intensive care unit. This was especially evident in the second child who took only 200 min to awake (plasma concentration 3315 ng ml⁻¹). This "tolerance" may have considerably shortened the time of recovery of both children.

In conclusion, this study confirms the clinical impression of a previous report (Booker, Beechey and Lloyd-Thomas, 1986), that midazolam is a useful drug for the sedation of children receiving intensive care. It appears that the majority of the children investigated by this study handled midazolam in a manner similar to adults. However, caution should be exercised in critically ill patients in whom hepatic function may be impaired.

ACKNOWLEDGEMENTS

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REFERENCES


