Intranasal midazolam for premedication of children undergoing day-case anaesthesia: comparison of two delivery systems with assessment of intra-observer variability

N. GRIFFITH, S. HOWELL AND D. G. MASON

Summary
Midazolam is often used for paediatric premedication. We have compared two methods of administering midazolam intranasally in 44 surgical day-case children allocated randomly to receive midazolam 0.2 mg kg\(^{-1}\) as drops or midazolam 0.1 mg kg\(^{-1}\) from an intranasal spray device. Behaviour was recorded on a four-point scale by the parent, nurse and anaesthetist. Coefficients were obtained representing the change in behaviour score. There was no significant difference in method of administration (coefficient 0.13, \(P=0.39\)). Children were significantly more distressed at the time of premedication and at the time of venous cannulation (coefficients 1.31 and 0.70) than at baseline. There was no significant difference in the assessments between observers. Midazolam by either method was equally effective but acceptability of the premedication was poor in both groups. Intranasal midazolam cannot be recommended as a method for routine premedication of young children. (Br. J. Anaesth. 1998; 81: 865–869).

Keywords: hypnotics benzodiazepine, midazolam; premedication, midazolam; anaesthesia, paediatric; anaesthesia, day case

In paediatric day-case anaesthesia, premedication may be required to minimize psychological stress or to control a distressed child. If used, it needs to be in an acceptable form, to have a rapid onset with minimal hangover effect and to have few side effects. Amnesia for transfer and entry to the operating theatre and a smooth induction may also be desired to reduce anxiety at subsequent visits.

Midazolam, a water soluble, short-acting 1, 4-benzodiazepine, may be administered by various routes. Oral and rectal routes are used widely and provide effective sedation. However, some authorities have expressed concern about the wide bioavailability when given by these routes, ranging from 18% to 44% with an appreciable first-pass effect.\(^1\)\(^\text{2}\) I.m. administration is painful and the sublingual route is effective but has poor compliance.\(^3\) The intranasal route for midazolam has been used since 1988 and has the advantage of rapid absorption directly into the systemic circulation with no first-pass effect and a bioavailability of 55–83%.\(^7\)\(^\text{10}\) However, the delivery method appears to be poorly tolerated and threatening, with poor retention of drops and drainage into the post-nasal space.\(^11\)

Midazolam 0.1–0.2 mg kg\(^{-1}\) by nasal drops from a syringe provides adequate plasma concentrations and good effect within 10–12 min.\(^12\)\(^\text{13}\) As a fine spray, the drug can be delivered well into the nasal cavity, avoiding spillage and swallowing seen with drops and thus allowing a smaller dose to be used.\(^10\) Our primary aim was to determine if application by spray delivery was practicable and if it would be less unpleasant while still being as effective as drops.

Assessing distress in children is subjective. We also compared assessments of each subject’s distress made by three different observers: the child’s parent, a ward nurse and the study anaesthetist (N.G.) using a numerical rating score modified from Davis and colleagues.\(^14\)

Patients and methods
After obtaining approval from the Institutional Ethics Committee and informed written consent from parents, we studied 44 children, weighing less than 30 kg, aged 1–8 yr. All patients were ASA I or II and were undergoing elective day surgery in the paediatric day unit. Patients were excluded if there was parental or child refusal or if there were nasal secretions.

The children were allocated randomly by the toss of a coin to receive commercially available i.v. midazolam (5 mg ml\(^{-1}\), Hypnovel, Roche) intranasally by one of two applicators. Group D received midazolam 0.2 mg kg\(^{-1}\) as drops from a 1-ml syringe (\(n=20\)) and group S received midazolam 0.1 mg kg\(^{-1}\) as a spray from a nasal pump (\(n=24\)), in each case corrected to the nearest 0.5 mg. A lower dose was given using the spray, as better delivery and absorption were expected with this route of administration, as shown by better bioavailability.\(^10\)

EMLA cream was applied to the dorsum of both hands. Resuscitation equipment was available, including flumazenil 0.5 mg ml\(^{-1}\). Premedication was administered in the treatment room on the ward by the study anaesthetist (N.G.) just before the patient went to theatre. The child sat facing forwards on the parent’s lap while their arms were gently restrained by one parental hand and the other hand used to tilt the forehead back 15°. Premedication was given by

N. GRIFFITH, MB, BCH, FRCA, D. G. MASON, MB, BS, FFARCS, Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford OX3 9DU. S. HOWELL, MA (CANTAB), MSC, MRCS (UK), FRCA, Sir Humphrey Davy Department of Anaesthetics, Bristol Royal Infirmary, Bristol BS2 8HW. Accepted for publication: June 23, 1998.
the study anaesthetist to one nostril using either a 1-
ml syringe or a nasal pump spray (Perfect-Valois UK
Ltd, Pump VP3/140 18ph White Plastic Gasket No
400, Diptube 32mm) and modified bottle into which
conveniently fitted a 2-ml midazolam 5 mg ml⁻¹
ampoule (fig. 1). The metered dose with each spray
had a volume of 0.1 ml equivalent to midazolam
0.5 mg.

Each child’s behaviour was scored on a four-point
scale presented on a printed card as follows: 1 = unafraid, calm, playing and relaxed; 2 = calm with
reassurance, suspicious; 3 = miserable, afraid, anxious;
4 = crying, clinging, combative. Scores were obtained
separately and independently from three observers:
parent, ward nurse responsible for the child and
N. G., at the following times: before premedication
(baseline), immediately after premedication, on
arrival in theatre and at cannulation.

The parent and N. G. were both present throughout
the study. They gave their scores for the effect of
the premedication immediately after administration
of midazolam. The nurse left the room before admin-
istration of midazolam and returned to give her score
approximately 3 min later. Thus the nurse was blind
to the mode of premedication and her score was
given slightly later than that of the parent and N. G.
She then accompanied the child to theatre with the
parent and N. G. Four different nurses were present
on the ward during the study, but the same nurse fol-
lowed through each child.

On arrival in the anaesthetic room, vein cannula-
tion was performed using a 22-gauge Venflon and i.v.
induction was performed in preference to inhalation
induction. Analgesia was provided with rectal
diclofenac 1 mg kg⁻¹ and local blocks where appropri-
ate. Any complications were noted.

Behaviour at induction was assessed by the anaes-
thesist, and that at recovery by the recovery nurse, as
either good or poor. Both were unaware of whether
or not the child had received premedication. The
child was sent to the ward when fully awake. Before
discharge home, the parents and child (if old
enough) were asked to comment on the acceptability
effectiveness of the route of premedication.

Data were analysed using STATA 5.0 from
Windows '95 running on a Dell Latitude XPl CD.
Descriptive statistics were produced for the two
patient groups. Median (range) values were reported
for continuous variables and proportions for catego-
rial variables. The groups were compared using
unpaired t tests for continuous variables and Fisher’s
exact test for categorical variables.

The effects of type of delivery system, observer and
time of observation were examined by multiple linear
regression modelling. Indicator variables were used
to identify treatment with drops, two of the observers
(the nurse and anaesthetist), and time periods after
baseline. This gave a regression model which
described the behaviour score for a child in terms of
a baseline value plus coefficients, indicating the deliv-
ery system, time period and observer:

Behaviour score =
baseline + observer₁(x) + observer₂(x) + ...etc.

As the nurse made her observation approximately
3 min after the parent and anaesthetist, an interac-
tion term was introduced to examine specific differ-
ences between the other observers at this time.
Coefficients were examined using a t test. P < 0.05
was taken as significant and robust standard errors
were used as repeated measures were being taken on
the same patient at different times.

The use of robust standard errors allows the
assumption of the independence of observations to
be relaxed. Conceptually they may be viewed as
being estimated by repeated sampling of the dataset
with replacement (as in the bootstrap method). In
STATA they are calculated by Huber’s method (also
known as the sandwich estimator of variance) which
allows robust standard errors to be calculated with-
out having to fit the model a large number of times.¹⁵

Results

We recruited 44 children: 20 children in the drops
group (group D) and 24 in the spray group (group S).
Only one child who had been randomized (group D)
refused the premedication. Five others did not
receive the complete dose: one in group D where the
drops were seen to drip out of the nares and four in
group S who moved before all the metered spray
doses had been administered. All patients were
included in the statistical analysis as the data were
analysed on the basis of intention to treat.

Both groups were similar in age, weight, previous
operations, type of anaesthesia and surgery, and
induction and recovery behaviour (table 1). No child
stayed in hospital overnight. The behaviour scores for
the two study groups, as given by the three observers,
are reported in table 2.
A linear regression model was generated to describe the data (table 3). The coefficients and confidence intervals (CI) in the equation were as follows: the constant in the equation indicating the score of a child in group S, at baseline, as observed by the parent, was 1.44 (95% CI 1.15–1.72); the coefficient for time of premedication was greatest, reflecting that this was an adequate model for the data.

The coefficients for premedication, arrival in theatre and cannulation were positive, indicating that the children were significantly more distressed at these times than at baseline. At the time of premedication, coefficients were 1.31 (95% CI 1.22–1.41, t = 4.3, 2 df, P < 0.0001), at the time of arrival in theatre, 0.09 (95% CI 0.09–0.10, t = 9.5, 1 df, P < 0.0001) and at the time of cannulation, 0.70 (95% CI 0.69–0.70, t = 32.3, 1 df, P < 0.0001). The coefficient for time of premedication was greatest, reflecting the fact that children were most distressed at this time. While statistically significant, the coefficient of 0.09 for arrival in theatre was not clinically significant.

There were no significant differences between the scores given by the three observers. For the nurse, coefficients were −0.17 (95% CI –0.52–0.18, t = –1.50, 2 df, P < 0.23) and for the study anaesthetist, −0.21 (95% CI –0.5–0.08, t = –2.3, 2 df, P < 0.11).

The nurse observing the child after premedication found the child to be less upset than the other observers. The interaction term was negative and highly significant (−0.79, 95% CI −0.8 to −0.49, t = −8.58, 1 df, P < 0.0001). The residuals from the linear regression model were normally distributed and their values were independent of the predicted values, indicating that this was an adequate model for the data.

Behaviour at induction was recorded as good by the case anaesthetist for 19 of 20 children in group D and for 19 of 24 children in group S. Similarly, behaviour on awakening was recorded by the recovery nurse as good for 17 of 20 children and for 20 of 24 children in groups D and S, respectively (table 1).

The majority of children found premedication administered by the nasal route unpleasant, whether given by spray or drops. Most complained of unpleasant taste and younger children dribbled. A smaller proportion complained of stinging in the nose, with younger children rubbing their noses—this was more common in group S (13 of 24 children compared with seven of 20 in group D). Half of the children in each group cried and only one of the 43 children neither cried nor complained.

On later questioning, 14 of 20 children in group D were old enough to comment and described the premedication as “horrible”. One had refused the premedication and five others were too young to comment but had cried and been upset. Of the 16 patients old enough to comment in group S, 15 described the premedication as “horrible” and one as “okay”. The other eight children were too young and had cried on administration. Only one child in group S, aged 4.5 yr, neither complained of the taste nor stinging, did not cry and described the premedication as okay.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Group D (n = 20)</th>
<th>Group S (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>4.3 (1.3–8.2)</td>
<td>4.8 (1–8.5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>17.3 (10.4–25.5)</td>
<td>17.9 (10–27.8)</td>
</tr>
<tr>
<td>Previous operation</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Method of induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I.v.</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Inhalation</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumcision</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Hernia repair/hydrocele</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Orchidopexy/PPV</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Umbilical hernia repair</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

| Behaviour at induction     |                 |                 |
| Good                       | 19              | 19              |
| Poor                       | 1               | 5               |
| Behaviour in recovery      |                 |                 |
| Good                       | 17              | 20              |
| Poor                       | 3               | 4               |

<table>
<thead>
<tr>
<th>Baseline score</th>
<th>Premedication score</th>
<th>Theatre arrival score</th>
<th>Cannulation score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>Drops (0.6)</td>
<td>Spray (0.6)</td>
<td>Drops (0.6)</td>
</tr>
<tr>
<td>Nurse</td>
<td>1.5 (0.5)</td>
<td>1.2 (0.5)</td>
<td>2.0 (0.9)</td>
</tr>
<tr>
<td>Anaesthetist (N. G.)</td>
<td>1.5 (0.6)</td>
<td>1.4 (0.5)</td>
<td>2.6 (1.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Robust standard error</th>
<th>t</th>
<th>P</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drops</td>
<td>0.13</td>
<td>0.13</td>
<td>1.00</td>
<td>0.39</td>
</tr>
<tr>
<td>Time of premedication</td>
<td>1.31</td>
<td>0.03</td>
<td>43.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time of arrival in theatre</td>
<td>0.09</td>
<td>0.0009</td>
<td>95.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time of cannulation</td>
<td>0.70</td>
<td>0.002</td>
<td>322.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Observer—nurse</td>
<td>–0.17</td>
<td>0.11</td>
<td>–1.50</td>
<td>0.23</td>
</tr>
<tr>
<td>Observer—anaesthetist</td>
<td>–0.21</td>
<td>0.09</td>
<td>–2.30</td>
<td>0.11</td>
</tr>
<tr>
<td>Interaction term = nurse observer for premedication</td>
<td>–0.79</td>
<td>0.09</td>
<td>–8.58</td>
<td>0.003</td>
</tr>
<tr>
<td>Constant</td>
<td>1.44</td>
<td>0.09</td>
<td>15.80</td>
<td>0.001</td>
</tr>
</tbody>
</table>
No child became excessively sleepy and there were no complications related to administration, although one child in group S had a minor nose bleed the following day.

Discussion

Minor surgery and day-case anaesthesia can cause great distress for both children and their parents. Previous surgery with possible frightening memories has been identified as a factor causing postoperative anxiety reactions; amnesia of these events is desirable in paediatric patients.16–18 Numerous authors have searched for the ideal paediatric premedicating agent and also for the best route of administration.6 7 11–13 20 25 Many do not discuss unpleasant taste, sneezing, stinging, coughing, swallowing or crying.6 7 11–13 20 25 Numerous authors have mentioned temporary distress, burning, an unpleasant taste suggesting that even as an aerosol the solution did not remain within the nasal cavity and reached the taste receptors in the oropharynx and on the posterior tongue via the post-nasal space. It is surprising that the drops did not cause a greater taste sensation than the spray, as more seemed to reach the mouth.

Administration as a spray is complicated by the need to keep the head still for multiple applications. For larger children of more than 20 kg, where four or more sprays of the 5-mg ml⁻¹ solution were needed, compliance was a real problem and movement and struggling between sprays led to loss of some of the solution. This was even more noticeable as the stinging was apparent immediately. A more concentrated solution would have allowed fewer sprays, but this could not be formulated through our pharmacy department, although a 40-mg ml⁻¹ solution was used in one other study.30 Transmucosal absorption depends on the physical and chemical properties of a solution; better absorption may be expected if midazolam was in a lipophilic vehicle at neutral pH unlike the hydrophilic form in which it exists. Secretions from nasal irritation may also alter absorption.

We used a four-point scoring system modified from Davis and colleagues.14 This was limited in that it allowed only two extreme scores and two intermediate scores. Also, the statistical analysis assumed that the points were evenly distributed on an interval scale. While we used a scoring system which had been used previously by other authors, a visual analogue scale would have helped obviate these problems. The difficulties with behavioural scoring systems are reflected by the fact that, while the scoring system showed that parents scored their child as more distressed in theatre, from the parental questionnaire, 36 of 44 parents felt that their child’s behaviour had improved by the time they arrived in theatre. Also, the case anaesthetist and recovery nurses felt that behaviour was good in the majority of children (table 1). This may reflect the subtle distinction between distress and behaviour. A child may be well behaved but terrified. However, it seems likely that our current tools for measuring distress in children are not perfect.

The study was not fully blinded as the logistics were such that the study anaesthetist also administered the premedication and therefore could not be blinded. Only the nurse was blinded to the route of premedication as it was considered to be unacceptable to exclude the parent from the room at that time. There was no placebo group as inclusion of such a group would have complicated the study design, but it would have allowed the efficacy of nasal midazolam by different applicators to be examined quantitatively.

In summary, midazolam was shown to cause significant distress at the time of intranasal administration, whether by drops or spray. This is subsequently remembered by children as an unpleasant experience and thus it cannot be recommended as a routine method of premedication in children.
References