Plasma Concentrations of Midazolam in Children Following Intranasal Administration

Eric J. Walberg, M.D.,* Robert J. Wills, Ph.D.,† Joanne Eckert, C.R.T.T.‡

Nasally administered midazolam appears to be a useful method for rapidly sedating children prior to the induction of anesthesia. We determined the peak plasma concentrations after intranasal administration of midazolam and compared this to plasma concentrations achieved after intravenously administered midazolam in 18 children between the ages of 14 months and 5 yr, who underwent elective closure of an asymptomatic atrial septal or ventricular septal defect. Preanesthetic medication was at the discretion of the attending anesthesiologist. Induction of anesthesia was with halothane in N₂O and O₂ via mask, and tracheal intubation was performed after the administration of fentanyl or sufentanil plus pancuronium. Anesthesia was maintained with these agents, and augmented with halothane or isoflurane. As soon as arterial access was established, the patient received 0.1 mg/kg of either intranasal or intravenous midazolam. Midazolam concentrations were measured by gas chromatography–mass spectrometry. Intranasal midazolam achieved its peak plasma concentration of 72.2 ± 27.3 ng/ml in 10.2 ± 2 min. Ten minutes after the administration of midazolam, the mean plasma concentration in the intranasal midazolam group was 57% of the concentrations in the group receiving midazolam intravenously. These results confirm the clinical impression that intranasal administration of midazolam rapidly achieves sedative plasma concentrations in children. (Key words: Anesthesia: pediatric. Hypnotics: midazolam. Pharmacokinetics. Premedication, midazolam: intranasal.)

THE PREOPERATIVE PERIOD is frequently an anxious and stressful time for children. Effective preanesthetic medication often permits a less traumatic separation of the child from his or her parents and can facilitate a smoother induction of anesthesia. A number of medications, including barbiturates, anticholinergics, opioids, sedatives, and benzodiazepines, alone or in various combinations, have been used to achieve these goals. In addition, different routes of administration, such as rectal, oral, and intramuscular, have been used. Recent reports describe the efficacy of the intranasal administration of both sufentanil† and midazolam.‡ Midazolam has been shown to be an effective preanesthetic medication in children when administered either orally or rectally, although studies of its pharmacokinetics when administered by these routes disclose a relatively slow onset, low peak concentrations, and limited bioavailability. This study delineates the peak plasma concentrations, and the time needed to achieve these concentrations, after intranasal administration of midazolam to children.

Materials and Methods

After obtaining approval of the institutional human subjects review board and parental consent, 18 subjects were enrolled in the study. These children were between the ages of 14 months and 5 yr, were ASA Physical Status 1 or 2, and were scheduled to undergo elective closure of an asymptomatic atrial septal or ventricular septal defect. At the discretion of the attending anesthesiologist, they received one or more of the following preanesthetic medications: morphine 0.1–0.2 mg/kg intramuscularly, scopolamine 0.05 mg/kg intramuscularly, and pentobarbital 3–4 mg/kg orally or rectally. Induction was with halothane in N₂O and O₂ via mask; tracheal intubation was performed after administration of fentanyl or sufentanil plus pancuronium. Anesthesia was maintained with these agents and augmented with halothane or isoflurane (always <1.0% inspired). Blood pressure, arterial CO₂ tension (PaCO₂), and core temperature were maintained throughout the study period at levels normal for the patient's age.

After percutaneous arterial cannulation, the first nine patients received 0.1 mg/kg midazolam intravenously, and the second nine received 0.1 mg/kg midazolam intranasally, in the form of drops at a concentration of 5 mg/ml. A 3-ml blood sample was obtained every 10 min in the intravenous group for the 1st h, and then every 15 min until the establishment of cardiac bypass (90 min total). In the intranasal group, samples were obtained at 1, 3, 5, 7, 10, 15, 20, 30, 40, 50, and 60 min, and then every 15 min until bypass (90 min total). Plasma was separated by centrifugation at 3,000 rpm × 10 min and then stored at −20°C until analyzed. An unpaired t test was used to compare the patient characteristics.

Midazolam Assay

Midazolam plasma concentrations were determined by a specific gas chromatographic–negative chemical ionization–mass spectrometric procedure. Fresh working solutions for each calibration curve were prepared in water.

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A saturated borate buffer was employed, and the extracting solvent was toluene: dichloromethane (7:3). The organic layer then was evaporated with air until dry. The residue was reconstituted in ethyl acetate and injected without forming a derivative, since only midazolam was to be analyzed. Hydrogen was the carrier gas. Instruments included a Finnigan 4500 gas chromatograph–mass spectrometer equipped with a fused silica gas chromatograph capillary column (DB1, J & W Scientific), linked to a SuperIncos® data system.

The assay sensitivity with 1.0 ml of sample was 1.0 ng/ml, and the assay was linear over a concentration range of 1.0–100 ng/ml. The overall intra- and interassay precisions were ±2.9 and ±6.7% relative standard error, respectively, determined at concentrations of 1, 5, 10, 50, and 100 ng/ml.

The maximum plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) after intranasal administration were read directly from the concentration versus time data.

## Results

The subject characteristics and their anesthetic management are listed in Table 1. There were no significant differences between the two groups with regard to age, weight, or surgical procedure. There was some spillage of the midazolam dose in two subjects (1 and 6 in Table 1). Since the amount spilled could not be quantified, these subjects were omitted from the calculations for peak concentration (C_{max}) but were included in the data used to determine time to peak level (t_{max}).

Intranasal midazolam, at a dose of 0.1 mg/kg, achieved a mean peak plasma concentration of 72.2 ± 27.3 ng/ml. The mean time required to achieve t_{max} was 10.2 ± 2 min. Ten minutes after intranasal administration of midazolam, the plasma concentration was 57% of that seen in the intravenous group after 10 min. The data for the intranasal group are displayed in Table 2, and the full concentration versus time data are shown in Figure 1.

### Discussion

These results support the clinical impression that intranasal midazolam rapidly achieves significant plasma concentrations. The t_{max} found in our study, 10.2 ± 2 min, is one fifth of that reported in children for midazolam administered orally (53 min)\(^7\) and one third (30 min)\(^7\) to two thirds (16 min)\(^8\) of the t_{max} for midazolam administered rectally. Plasma midazolam concentrations exceeded the proposed therapeutic threshold for sedation in adults (40 ng/ml)\(^9\)–\(^11\) as early as 5 min after intranasal administration (Figure 1) and continued to exceed this level for >30 min. Although the threshold for sedation in children is unknown, it is likely that it is higher than that in adults, based on children's decreased sensitivity to midazolam used as an induction agent.\(^12\) Saint-Maurice et al. found that all of their patients had “satisfactory” inductions; their average plasma concentrations were ≈65 ng/ml, 30 min after rectal administration.\(^8\) With the intranasal dose used clinically (0.2 mg/kg), the average peak plasma concentrations should be about two to three times the 40-ng/ml sedation threshold in adults, and at least two times the plasma concentration that resulted in a satisfactory inhalation induction in children.\(^8\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>3.0 ± 1.4</td>
<td>12.8 ± 3.3</td>
<td>ASD-3</td>
</tr>
<tr>
<td>Intensal</td>
<td>2.1 ± 0.8</td>
<td>11.8 ± 2.9</td>
<td>ASD-3</td>
</tr>
</tbody>
</table>

ASD = atrial septal defect; VSD = ventricular septal defect; following number indicates number of patients with lesion.

### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Subject</th>
<th>C_{max} (ng/ml)</th>
<th>t_{max} (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43.7</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>74.1</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>94.2</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>38.0</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>106</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>95.1</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>54.1</td>
<td>10</td>
</tr>
</tbody>
</table>

* Subjects with incomplete midazolam dose (see text).
The experimental conditions in this study differ from the usual clinical applications of intranasal midazolam in that the patients were already anesthetized at the time of midazolam administration and had congenital heart defects. Since we were most interested in $t_{\text{max}}$ and $C_{\text{max}}$, we needed to obtain a large number of 3-ml samples over a short period of time in small (7–18 kg) children. Ethically, we felt that the only group of children who could meet these requirements were patients undergoing cardiac surgery, since they would have an intraaerial catheter placed and would receive a blood transfusion (blood pump prime) regardless of our study. It may be argued that the anesthetic that had been administered and the subjects' cardiac conditions may have increased the uptake of nasally administered midazolam.

However, this is unlikely for several reasons. Preoperative sedation is administered usually to children who are agitated or frightened or both. One would expect such children to have cardiac outputs higher than children who are anesthetized with opioids, potent inhalation agents, and muscle relaxants. In addition, our subjects' cardiac lesions tended to reduce systemic cardiac output, although their pulmonary blood flow was markedly increased. Scopolamine and atropine administered as a preanesthetic medication may result in a dry nasal mucosa.

These conditions would tend to reduce the uptake of a drug; however, the direct effect of either inhalation or intravenous anesthesia on nasal mucosal blood flow is unknown. One can only speculate that since the nasal mucosa is richly perfused, and that absorption from the nasal mucosa is determined primarily by the physical and chemical properties of the drug involved, small changes in regional blood flow through the nasal mucosa secondary to anesthesia would make little difference in uptake of the drug. In a model of nasal uptake of compounds in rats, there was no difference in the rate of uptake of propranolol with or without barbiturate anesthesia. If there were large changes in mucosal blood flow, then it is conceivable, but unlikely, that the uptake of midazolam administered nasally could be altered in either direction. Clinically, children appear to have appreciable sedation within 5 min of receiving intranasal midazolam, and maximal sedation within 10 min. Therefore, the time course of the sedative effects of intranasal midazolam paralleled our findings. In our clinical experience, an upper respiratory infection with copious nasal secretions has been the only condition that has resulted in inadequate sedation when midazolam is administered intranasally.

It is conceivable that intranasal administration of midazolam would yield greater degrees of sedation than plasma concentrations of the drug would imply. There is some evidence in humans that certain drugs may achieve proportionately higher concentrations within the brain or a faster onset when administered nasally than intravenously. It is speculated that these compounds are absorbed into the brain and cerebrospinal fluid directly through the cribiform plate. Confirmation in animal models is lacking, and any possible application to children is completely unknown.

The rapid onset of relatively high plasma concentrations obtained after intranasal administration of midazolam offers significant advantages over orally or rectally administered drug and supports the claim that it may be a useful method for expeditiously sedating children. It may be particularly appealing as an alternative to rectal barbiturates, with their prolonged absorption and slow elimination, for premedicating children in whom a rapid recovery or awake extubation or both is desirable.

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§ Hussain A: Personal communication.

References