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# ***Transmucosal Administration of Midazolam for Premedication of Pediatric Patients***

## ***Comparison of the Nasal and Sublingual Routes***

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**Background:** Nasal transmucosal midazolam is effective for premedication of pediatric patients; however, 61–74% of these patients cry at nasal drug administration. Sublingual benzodiazepines, including midazolam, are effective in adults. The current blinded randomized study compared acceptance of and behavioral responses to transmucosal midazolam administered *via* the intranasal and sublingual routes.

**Methods:** Ninety-three patients aged 0.5–10 yr were stratified by age: 30 infants and toddlers, 0.5–2 yr; 39 preschoolers, 2.1–5 yr; and 24 school age, 5.1–10 yr. They were randomized to receive 0.2 mg/kg of midazolam in the nose or under the tongue without or with additional flavoring. For the group receiving sublingual flavored midazolam, the syringe tip was dipped in candy flavor and sugar. Duration of crying and compliance with instructions for sublingual drug administration were recorded. Hemoglobin oxygen saturation by pulse oximetry and sedation score were recorded by three observers before drug administration, at 2.5-min intervals for 10 min, at separation from parents, and during induction with halothane in O<sub>2</sub>.

**Results:** Children accepted midazolam administered *via* the sublingual route better than that given intranasally. In children not crying before drug administration, the frequency and duration of crying was greater following intranasal compared with sublingual administration (71% *vs.* 18% ( $P < 0.0001$ ))

and  $48 \pm 56$  *vs.*  $25 \pm 49$  s ( $P = 0.004$ ), respectively). Lack of total compliance with instructions for sublingual administration did not alter drug effect, and there were no differences between the three study groups in maximum sedation, response to separation from parents, and behavior at induction of anesthesia; 80% displayed adequate or excellent behavior. Finally, the addition of candy flavor did not improve acceptance of or compliance with sublingual midazolam administration.

**Conclusions:** Sublingual administration of midazolam is as effective as, and better accepted than, intranasal midazolam as a preanesthetic sedative in children. (Key words: Anesthesia, pediatric; premedication. Anesthetic techniques: transmucosal drug administration. Hypnotics, benzodiazepine: midazolam.)

PREANESTHETIC medication may reduce the risks of adverse psychological<sup>1,2</sup> and physiologic<sup>3,4</sup> sequelae of induction of anesthesia in a distressed child. The water-soluble benzodiazepine, midazolam, has been demonstrated to be a safe and effective preanesthetic anxiolytic agent.<sup>5–7</sup> However, the orogastric,<sup>5</sup> intramuscular,<sup>6</sup> and rectal<sup>8–10</sup> routes of administration of this compound are associated with disadvantages.<sup>11–13</sup> Intranasal administration of midazolam has been of interest because of the rapid, reliable onset of action, predictable effects, and avoidance of injections.<sup>7,13–15</sup> However, we have noted that children object to the burning sensation and unpleasant taste of intranasal midazolam as vigorously as they do to an injection. Because many medications are well absorbed from the sublingual<sup>16–20</sup> mucosa, we conducted a randomized, prospective, blinded study to compare acceptance and efficacy of sublingual and intranasal administration of midazolam as a preanesthetic medication in children before inhalation induction.

### **Materials and Methods**

After approval from the Clinical Investigation Committee and informed parental consent, 93 patients aged

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6 months to 10 yr were studied. All ASA physical status 1 and 2 inpatients and outpatients scheduled for elective surgery were eligible for study. Children were excluded if they required an intravenous induction, or if they had an upper respiratory infection. Eligible patients were stratified into three age groups: infants and toddlers, 0.5–2 yr (n = 30); preschool children, 2.1–5 yr (n = 39); and school-age children, 5.1–10 yr (n = 24). They were randomly assigned in blocks of three to one of the following treatment groups: intranasal (N, n = 31), sublingual (S, n = 31), and flavored sublingual (S+, n = 31).

To prevent unblinding of the behavior evaluators caused by the strong smell of the candy flavor essence (Lorann Oils, Inc., Lansing, MI) used to mask the taste of midazolam in the flavored sublingual group, each child's anesthesia mask was painted with the flavor of the child's choice before drug administration. A pulse oximeter probe was placed on all children, and Sp<sub>O</sub><sub>2</sub> and heart rate were recorded continuously from the time of probe placement through completion of induction. Resuscitative equipment was immediately available at the bedside. An anesthesia attending or resident not involved in the management of the patient or in gathering data for the study gave each child 0.2 mg/kg of midazolam (5 mg/ml).<sup>7,14</sup>

For children randomized to receive intranasal midazolam, undiluted drug was rapidly applied to the mucosa of one nostril using a syringe from which the needle had been removed, as previously described.<sup>14</sup> Children assigned to receive sublingual medication were first asked to place the tip of the tongue to the back of the upper teeth. Undiluted drug was then placed under the tongue, the child was asked to close their mouth, and was instructed "Don't swallow!"; at 30 s, the child was permitted to swallow the medication. For flavored midazolam, the tip of the filled syringe was dipped in the candy flavor essence chosen for the mask, then dipped in granulated sugar. As an additional attempt to mitigate the unpleasant taste of the midazolam, all children were offered an opportunity to lick a cotton-tipped applicator dipped in sugar. The duration of crying after drug application and of sublingual drug retention before swallowing were recorded.

During the 10-min interval between drug administration and separation from parents, the anesthesiologists caring for the patient encouraged the parents to engage the child in a favorite activity. At 10 min, the child was separated from the parents and taken to the operating room. Inhalation induction was accom-

plished with graded increments of halothane in oxygen. Anesthesia was maintained with 70% nitrous oxide, halothane, and oxygen *via* mask or endotracheal tube as appropriate.

#### *Evaluation of Drug Efficacy*

Our previous modification<sup>14</sup> of Wilton's sedation score<sup>7</sup> was used to grade responses to induction (table 1). Three independent behavior assessments were performed by an attending anesthesiologist, by an anesthesia resident or a nurse anesthetist, and by an anesthesia-trained observer not involved in the care of the patient at the following nine times: before and after an attempt to place a pulse oximeter probe, at 2.5-min intervals for 10 min after drug application, at separation from parents, at arrival in the operating room, and during induction of anesthesia. All evaluators were blind to the route of drug administration. The interval between drug application and the child's first smile was recorded. The independent observer recorded the incidence of premature ventricular contractions and laryngospasm, physiologic evidence of excitement during induction.

#### *Summary Description*

We combined indices of safety and efficacy to formulate a summary description of the separation-induction period.<sup>14</sup> Excellent conditions are defined as no display of anxiety (no median behavior score < 3) and Sp<sub>O</sub><sub>2</sub> > 95%. Adequate conditions are defined as minimal crying (no median behavior score < 2) or mild desaturation (Sp<sub>O</sub><sub>2</sub> 90–95%). Inadequate conditions are defined as the presence of a behavior score of 1, or a change in the anesthetic plan because of inadequate sedation.

**Table 1. Behavior Scoring System**

Criterion	Score
Agitated: clinging to the parent and/or crying	1
Alert: awake but not clinging to the parent; may whimper but not cry; anxious	2
Calm: sitting or lying with eyes open; relaxed	3
Drowsy: eyes closed but responds to minor stimulation	4
Asleep: does not respond to minor stimulation	5

Modified from Wilton.<sup>7</sup>

Scores were recorded independently by an attending physician, a resident or nurse-anesthetist, and an anesthesia-trained observer before (baseline) and after (pre-drug) oximeter probe placement, every 2.5 min for 10 min after nasal drug application, and at separation from parents, arrival in operating room, and induction of anesthesia.

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*Data Analysis*

Data other than behavior scores are reported as frequency (%) or mean  $\pm$  SD. The median of the three behavior scores at each time was considered to represent the child's behavior. The child's behavioral response to stress (pulse oximeter placement, separation from parents, and induction of anesthesia) was quantified by one-sample Wilcoxon tests comparing each child's behavior to that recorded just before the stress. Valid measurements of abstract phenomena such as anxiety are difficult to achieve; thus, we have made a variety of assessments.

Comparability of the study groups was confirmed by ANOVA and chi-square analysis of demographic and historic factors, by chi-square analysis of the frequency of crying before drug administration, and by the behavioral response to pulse oximeter placement.

Patients' acceptance of the medication was evaluated by comparing the incidence and duration of crying in response to drug administration with chi-square and Kruskal-Wallis tests, respectively. The same tests were used to compare the indices of compliance with instructions for sublingual administration: the presence or absence of spitting or early swallowing of the medication, and the duration of midazolam retention.

The relative efficacy of the midazolam was quantified by chi-square comparison of the incidence of smiling within 10 min of midazolam administration and of the incidence of crying at separation from parents and at induction of anesthesia. In addition, one-sample Wilcoxon tests were used to quantify the change in apparent anxiety during the 10-min period between drug administration and separation from parents, and by the behavioral responses to separation and induction of anesthesia. Two-sample Wilcoxon tests were used to compare the effects of the routes of administration on behavior at each time point. A chi-square test was used

to compare the overall conditions during the separation-induction period.

Evaluation of the age differences in all the behavioral responses above were conducted as part of a continuing attempt to arrive at optimal outcome variables for pre-medication studies. As part of ongoing validation of the behavior scoring methodology, the kappa-like statistic  $\kappa_{sav}$  was used to estimate interobserver reliability;<sup>14</sup> mean  $\kappa_{sav}$  ( $\pm$  SD) over all time points is reported. Stepped-up reliability for behavior scores was calculated using the Spearman-Brown formula.<sup>21</sup> A *P* value of  $<0.05$  was considered significant.

**Results***Patient Population*

Treatment groups (within and across age groups) were not different from each other with respect to age, weight, gender, ASA physical status, or the number of previous operations. By chance, children who had had previous experience with intranasal medication were more commonly assigned to the sublingual group (*P* = 0.018).

*Pre sedation Behavior*

Infants and children (with parents present) were scored before and after oximeter probe placement, an index of the behavioral response of unmedicated children to a small standard stress. Overall, within the sublingual treatment group, and within the youngest age group, behavior scores after probe placement were significantly lower (increased anxiety) than they were before (*P* < 0.05). Patients who had been assigned the sublingual route showed greater anxiety than those in the intranasal group: they had lower behavior scores (*P* = 0.04) and included all 11 of the patients who were crying before drug administration (*P* = 0.03).

*Response to Drug Administration*

Eighty-two of the 93 children were not crying before drug administration. Of these, 71% cried in response to intranasal administration of midazolam, *versus* only 18% after sublingual application of medication (table 2, *P* < 0.001). Within age groups, only preschool children showed a significant difference in the incidence of crying between treatment groups (*P* < 0.001). Patients who received intranasal midazolam also cried significantly longer than those to whom it had been given sublingually, ( $48 \pm 56$  vs.  $25 \pm 49$  s, *P* = 0.004).

**Table 2. Crying in Response to Midazolam Application**

Age Group	Intranasal	Sublingual (Plain)	Sublingual (Flavored)
Infants	80% (8/10)	43% (3/7)	25% (2/8)
Preschool	77% (10/13)*	10% (1/10)	10% (1/10)
School age	50% (4/8)	13% (1/8)	13% (1/8)
Total	71% (22/31)*	20% (5/25)	15% (4/26)

The incidence of crying at the time of administration of midazolam in patients who were not previously crying.

\* *P* < 0.001 intranasal *versus* sublingual (with or without flavor; chi-square analysis).

### Compliance with Instructions

Fifteen children of all ages spat out at least some of the midazolam, even when it was administered intranasally. In addition, half of the children receiving sublingual midazolam did not comply with the instructions for administration and either spat out or swallowed the medication substantially before the 30 s sublingual retention period had elapsed (at 20 s, table 3). Compliance was greater in school age children compared with infants and preschoolers. Addition of candy flavoring did not affect either index of compliance. Overall, 38 of the 62 patients who received midazolam *via* the sublingual route did not comply with some or all of the instructions for its administration.

### Sedation and Separation from Parents

Eighty-five percent of the patients (87% of infants, 77% of pre-school, and 96% of school-age children) smiled within 10 min of midazolam administration. There was no difference in the incidence of smiling between age or treatment groups. At the point of maximum anxiolysis (parents still present, 10 min after the drug was administered to children of all ages), midazolam administered by the sublingual route had produced a significant decrease in apparent anxiety ( $P < 0.03$ ) to the point that the difference in the treatment groups' behavior measured after pulse oximeter probe placement was no longer present.

The incidence of crying at separation from parents (11 min after drug administration) was low (8%, 3% in the intranasal and 10% in the sublingual groups,  $P = NS$ ). Within age groups, behavior scores were not

**Table 3. Noncompliance with Instructions for Sublingual Administration**

Treatment Group	Infants	Preschool	School Age	Total
<b>Plain</b>				
Retained (s)	10 ± 10	16 ± 13	29 ± 10	18 ± 13
Early swallow	86% (6/7)*	50% (6/12)	13% (1/8)	48% (13/27)
<b>Flavored</b>				
Retained (s)	12 ± 9	17 ± 13	30	19 ± 12
Early swallow	78% (7/9)*	62% (8/13)*	0 (0/8)	50% (15/30)
<b>Total</b>				
Retained (s)	11 ± 9*	16 ± 13*	29 ± 7	19 ± 13
Early swallow	81% (13/16)*	56% (14/25)*	6% (1/16)	49% (28/57)

The duration of sublingual midazolam retention (s; mean ± SD) and the incidence of swallowing <20 s after midazolam administration. There was no difference in retention or swallowing between plain or flavored treatment groups (Kruskal-Wallis and chi-square analysis, respectively, all ages together or within age groups).

\*  $P < 0.05$  versus corresponding group of school age children.

**Table 4. The Influence of Compliance with Instructions on Adequate Behavior**

Compliance	Infants	Preschool	School Age	Total
Compliant	100% (2/2)	100% (8/8)	93% (13/14)	96% (23/24)
Partially compliant	64% (9/14)	88% (14/16)	100% (1/1)	77% (24/31)
Noncompliant	75% (3/4)	0 (0/2)	0 (0/1)	43% (3/7)*

The relative number of patients whose behavior was adequate (see text for definition) throughout the period of "stress" (separation from parents through induction of anesthesia). Patients who did not spit any of the medication and who swallowed after at least 20 s of sublingual midazolam retention were defined as "compliant"; those who either spat out the medication or who swallowed early were defined as "partially compliant"; and those who both spit and swallowed early were "noncompliant."

\*  $P < 0.05$  versus compliant; chi-square analysis).

significantly different from those recorded at 10 min. However, with all age groups combined, children who received sublingual midazolam, unlike those in the intranasal group ( $P = NS$ ), showed an increase in apparent anxiety in response to the stress of separation from parents ( $P = 0.01$ ). Similarly, school-age children treated with sublingual midazolam showed more anxiety at separation than those who received the drug intranasally ( $P = 0.04$ ).

### Induction of Anesthesia

The behavior scores during inhalation induction (15 ± 2 min after drug administration) of children who received midazolam by either route were maintained or improved compared with those observed before its administration. Seventy-five (81%) of the children did not cry at the time of inhalation induction. There was no difference between the groups receiving intranasal or sublingual midazolam in the incidence of crying at induction of anesthesia.

### Effect of Compliance on Behavior at Separation and Induction

Almost all (23/24) children who complied completely with the instructions for sublingual midazolam administration (*i.e.*, they neither spat nor swallowed early) demonstrated adequate behavior at separation from parents and induction of anesthesia (table 4). In contrast, over half of those who both spat out some of the medication and swallowed the remainder early did not have adequate drug effect ( $P < 0.05$  vs. compliant, chi-square). Children who partially complied with instructions (*i.e.*, they either spat or swallowed early) showed an intermediate effect; however, 77% (24/31)

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demonstrated adequate behavior ( $P = 0.12$  vs. compliant, chi-square).

### Safety

Only one midazolam-treated patient had  $Sp_{O_2} = 93\%$  before induction, and one had laryngospasm during induction of anesthesia. No patient had PVCs noted during induction or intubation.

### Summary Description

Overall, there was no difference between the intranasal and sublingual routes of administration in the efficacy or safety of midazolam (table 5).

### Evaluation of Behavior Scoring System

There were 837 time points (sets) at which each of the three observers could record a score. Ninety-eight percent of the data sets were complete with 3 observations per set; the remaining 18 contained 2 observations. There was no difference in completeness of data sets between age or treatment groups. The estimated interobserver reliability ( $r_{sav}$ ) over all time points was  $0.74 \pm 0.15$  and  $0.82 \pm 0.09$  for the intranasal and sublingual-treated patients, respectively; reliability was similar in each age and treatment group. If the mean of the three observers' scores is used as an index

**Table 5. Overall Efficacy and Safety of Transmucosal Midazolam**

Group	n	Excellent	Adequate	Inadequate
Infants				
IN	10	20% (2/10)	50% (5/10)	30% (3/10)
SL	20	45% (9/20)	25% (5/20)	30% (6/20)
Preschool				
IN	13	77% (10/13)	15% (2/13)	8% (1/13)
SL	26	69% (18/26)	15% (4/26)	15% (4/26)
School age				
IN	8	38% (3/8)	25% (2/8)	38% (3/8)
SL	16	50% (8/16)	38% (6/16)	13% (2/16)
Total				
IN	31	48% (15/31)	29% (9/31)	23% (7/31)
SL	62	56% (35/62)	24% (15/62)	19% (12/62)

Behavior scores at separation from parents, arrival in the operating room, and induction of anesthesia, as well as  $Sp_{O_2}$  throughout this period, evaluation of chest wall compliance, and change in anesthetic plan due to inadequate sedation were grouped and rated without knowledge of drug treatment group. Each patient's record was rated as the least favorable of the following: 1) excellent (no median score  $<3$  and  $Sp_{O_2} >95\%$ ), 2) adequate (all median scores  $>2$  and/or  $Sp_{O_2}$  90–95%), 3) inadequate (a median score  $<2$  or change in anesthetic plan due to inadequate sedation).

of behavior, overall interobserver reliability increases to 0.90 and 0.93 for intranasal and sublingual groups, respectively.

### Discussion

This blinded, randomized study directly compared the acceptance and efficacy of a single, relatively low, dose of oral transmucosal midazolam to the same dose administered intranasally. Children clearly preferred sublingual to intranasal administration; however, the addition of candy flavor essence and sugar did not improve acceptance of the sublingual medication. Ten minutes after drug administration, most children were able to undergo the stresses of separation from parents and inhalation induction of anesthesia with minimal or no evidence of anxiety. These results occurred despite the fact that, by chance, children assigned to receive sublingual midazolam displayed more distress before drug administration than those who were to receive it intranasally, and that less than half of the children totally complied with the instructions for sublingual drug administration. The absence of a placebo control group reflects the conviction of the investigators that withholding a preinduction agent for the sake of the study would not be justified.

Application of drugs to oral, nasal, or rectal mucosa has long been used to produce local and/or systemic effects from a variety of cardioactive, analgesic, sedative, and other drugs.<sup>4,8,16–19,22</sup> The rich blood supply of the sublingual mucosa allows rapid absorption of drugs directly into the systemic circulation. Absorption depends on the time that the drug is adjacent to the mucosal surface (residence time), local pH (usually 6.2–7.4), saliva flow, and physicochemical characteristics of the drugs themselves and of the chosen site.<sup>17,18</sup> The known aqueous solubility of midazolam at acidic pH allows it to maintain a high concentration in salivary fluids (usual pH = 6–7). Previous work has shown that, like other benzodiazepines,<sup>19,22</sup> the bioavailability of sublingually administered midazolam was substantially greater than that administered orogastrically.<sup>23</sup> Because only 40–50% of an orogastrically administered dose reaches the systemic circulation intact because of the extensive first-pass hepatic metabolism of the drug,<sup>24</sup> we chose to test the anxiolytic efficacy of a sublingual dose of midazolam previously shown to be effective when administered by the nasal transmucosal route,<sup>7,14</sup> using a dose less than half of that recommended for orogastric administration.<sup>5</sup> The current methods do not

allow differentiation between drug absorbed through the sublingual mucosa and that absorbed from the stomach. However, if one assumes 50% first-pass metabolism to a metabolite with lower biological activity than midazolam,<sup>24</sup> and considers the fact that nasal application of a lower dose was not effective,<sup>7</sup> it seems likely that transmucosal absorption accounted for much of the total effect of sublingually administered drug. The characteristics of transmucosal absorption at various sites<sup>18</sup> and of mucosal cells<sup>25</sup> should be studied to define absorption mechanisms and optimize uptake.

The signs of anxiety shown by unmedicated children (particularly infants) with parents present to the non-painful stress of pulse oximeter probe placement are similar to, although not as extensive as, those we documented previously (17% vs. 33% appeared more anxious after pulse oximeter probe placement; 12% vs. 23% were crying before drug administration).<sup>14</sup> Perhaps this change reflects the effect of a hospital policy, instituted shortly after the beginning of data collection for this study, that allowed a substantial decrease in fasting duration. Hunger is one of the anxiety-producing factors that impact on children preoperatively. Our experience would then parallel that of Schreiner *et al.*, who described a substantial decrease in "irritability" in children allowed clear liquids up to 2 hr preoperatively.<sup>26</sup>

As we had documented previously,<sup>14</sup> intranasal application of midazolam was followed by a substantial incidence and duration of crying. The current results confirm that most children consider intranasal application of midazolam very unpleasant. Although the patients who received sublingual midazolam were more anxious than those in the intranasal group before the drug was given, children found sublingual administration substantially more acceptable. Unfortunately, the method described above to improve the taste of the midazolam did not appear to be successful. Subsequently, however, other approaches to the problem of palatability have been described.<sup>27</sup>

It comes as no surprise that school-age children followed the instructions for sublingual administration more effectively than younger patients. Neither is it unexpected that more than half of those who did not comply with either aspect of the instructions appeared distressed at separation from parents and induction of anesthesia. In a clinical situation, it might be advisable to repeat sublingual administration in noncompliant patients or to choose an alternative route of administration. We were pleased to find, but did not expect,

that three-fourths of the patients who did not comply with one portion of the instructions also had adequate drug effect. It is likely that the high (5 mg/ml) drug concentration applied, and the residence time at least as long as that achieved by nasal application, allowed sublingual absorption of adequate amounts of midazolam.

Valid measurements of abstract phenomena, such as anxiety, are difficult to achieve, and it is particularly important to search for differences in a situation in which one is trying to demonstrate a lack of difference between two clinical interventions. Therefore, we have made a variety of measurements and statistical comparisons. Taken alone, the increase in apparent anxiety in response to the stress of separation from parents could be interpreted as failure of the efficacy of sublingual administration of midazolam. However, this isolated result, seen in a group of patients who showed a clear difference in baseline anxiety, no difference in crying at separation, and no difference in any behavioral measure at induction of anesthesia, does not support that conclusion.

The availability of multiple drug administration techniques allows anesthesiologists the flexibility to provide optimal management for each clinical situation. Clearly, infants and children prefer sublingual to intranasal administration of midazolam. Because there is no substantial difference between the routes as to the drug's effects on behavior at separation from parents and induction of anesthesia, sublingual administration should be given serious consideration when transmucosal administration of midazolam is indicated. Further work is needed to achieve a more palatable medication- or drug-delivery system. When premedication does not taste so unpleasant, it is likely that more children will comply with instructions for administration, and the incidence of beneficial effects will increase.

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