A Comparison of Three Doses of a Commercially Prepared Oral Midazolam Syrup in Children

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Midazolam is widely used as a preanesthetic medication for children. Prior studies have used extemporaneous formulations to disguise the bitter taste of IV midazolam and to improve patient acceptance, but with unknown bioavailability. In this prospective, randomized, double-blinded study we examined the efficacy, safety, and taste acceptability of three doses (0.25, 0.5, and 1.0 mg/kg, up to a maximum of 20 mg) of commercially prepared Versed® syrup (midazolam HCl) in children stratified by age (6 mo to <2 yr, 2 to <6 yr, and 6 to <16 yr). All children were ASA class I–III scheduled for elective surgery. Subjects were continuously observed and monitored with pulse oximetry. Ninety-five percent of patients accepted the syrup, and 97% demonstrated satisfactory sedation before induction. There was an apparent relationship between dose and onset of sedation and anxiolysis ($P < 0.01$). Eight-eight percent had satisfactory anxiety ratings at the time of attempted separation from parents, and 86% had satisfactory anxiety ratings at face mask application. The youngest age group recovered earlier than the two older age groups ($P < 0.001$). There was no relationship between midazolam dose and duration of postanesthesia care unit stay. Before induction, there were no episodes of desaturation, but there were two episodes of nausea and three episodes of emesis. At the time of induction, during anesthesia, and in the postanesthesia care unit, there were several adverse respiratory events. Oral midazolam syrup is effective for producing sedation and anxiolysis at a dose of 0.25 mg/kg, with minimal effects on respiration and oxygen saturation even when administered at doses as large as 1.0 mg/kg (maximum, 20 mg) as the sole sedating medication to healthy children in a supervised clinical setting.

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Midazolam is the most commonly used oral preanesthetic medication for children (1). Before the development of a commercially prepared syrup, oral midazolam formulations were prepared by mixing the IV midazolam product with a variety of additives to mask the bitter taste (2,3). Because the fat solubility of midazolam is pH dependent (4–6), nonstandard oral formulations prepared with adjuvants with differing pH and dilutions are likely to have unpredictable absorption characteristics that may result in variability in drug dose response. Most prior studies of oral midazolam reported that doses from 0.5 to 1.0 mg/kg were needed to achieve satisfactory anxiolysis and patient cooperation (2,3,7–11). The purpose of this study was to examine the safety, efficacy, and dose response of a commercially prepared oral midazolam formulation with consistent bioavailability and pH characteristics. A secondary purpose was to collect adequate efficacy and safety data for product labeling for infants and children. This prospective, randomized, double-blinded, parallel-group study evaluated the perioperative effects of a single administration of three oral midazolam doses. A placebo-controlled trial was deemed unnecessary (12) because the efficacy of the IV formulation administered orally had previously been established (3,9,10,13).

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Methods

The study was approved by the IRBs of nine participating centers. Written, informed consent was obtained for each child; assent was obtained from children older than 7 yr. Children were stratified into three groups by age (6 mo to <2 yr, 2 to <6 yr, and 6 to <16 yr) and further randomized in block sizes of six within each age group to receive one of three doses of oral midazolam syrup.

Versed® syrup (2 mg/mL) (Roche Laboratories, Inc., Nutley, NJ) is cherry flavored and compounded with sorbitol, glycerin, citric acid anhydrous, sodium citrate, sodium benzoate, sodium saccharin, artificial cough syrup flavor, artificial bitterness modifier, and water, with the pH adjusted to approximately 3 with hydrochloric acid (4). Midazolam doses of 0.25, 0.5, and 1.0 mg/kg, up to a maximum of 20 mg, were dispensed to blind the dose administered from those performing patient assessments.

Patients (ASA class I–III) scheduled for elective surgical procedures were candidates for study. Exclusion criteria included seizure disorders, gastrointestinal disorders that might affect absorption, and any medical condition that could compromise the safety of the patient or interfere with the interpretation of the results. Because midazolam is a known substrate of the cytochrome P450 3A4 enzyme system (14,15), patients taking known cytochrome P450 3A4 inhibitors (e.g., grapefruit juice, imidazole derivatives, erythromycin, clarithromycin, or cimetidine) (16,17) or cytochrome P450 3A4 inducers (e.g., phenobarbital, phenytoin, rifampin, or corticosteroids) were excluded (18–20).

Clinical responses (sedation, anxiolysis, cooperation, and acceptability of taste), adverse effects (e.g., respiratory, hemodynamic, and others), and recovery were assessed by an observer blinded to midazolam dose. Safety was assessed by continuous oxygen saturation monitoring and observation. Vital signs (blood pressure, pulse, and respiratory rate) were recorded before drug administration (baseline) and then every 10 min until the induction of anesthesia and again in the postanesthesia care unit (PACU) until a Steward Post-Anesthesia Recovery Score of 6 was achieved (21). There was no attempt to control for surgical procedure or additional drugs administered for the conduct of anesthesia because the primary end points for the study were directed at patient pharmacodynamic responses before induction. We believed that this type of study would be the most generalizable because it closely reflected standard anesthetic practices.

Sedation was assessed with a five-point scale (alert/active = agitated, moving, physical or verbal display of apprehension; upset/wary = tearful, may be clinging; relaxed = calm, silly, responds readily to commands or gentle stimulation; drowsy = easily arousable, responds readily to mild shaking or prodding; asleep = unarousable, does not respond to mild shaking or prodding) (22). Sedation assessments were made at baseline, then at 10-min intervals for up to 45 min unless the patient was deemed acceptable for transport to the operating room. A score of 3 or higher was considered satisfactory. Sedation data were examined both for onset, time of maximal sedation score within 30 min of baseline, and time to satisfactory sedation scores.

Anxiolysis was assessed on a four-point scale (poor = afraid, combative, crying, restrained; fair = fearful, moderate apprehension; good = slightly fearful, easily calmed by strangers, noncombative; excellent = no fear or apprehension displayed; not applicable = patient asleep) (3). Anxiolysis was assessed at the same intervals as sedation scores. An anxiety score was also recorded at the time of attempted separation from parents (parents were offered the opportunity to accompany their child to the operating room, but a sham or real separation was attempted with all children). An anxiety score of 3 or 4 was considered satisfactory. The timing of attempted child-parent separation, which occurred from 15 to 45 min after premedication, was determined by operating room availability and patient responses.

Cooperation was assessed with a four-point scale (poor = strongly refuses intervention; fair = considerable effort required to achieve compliance with intervention; good = accepts intervention reluctantly; excellent = accepts intervention readily; not applicable = patient asleep). A cooperation score of 3 or 4 was considered satisfactory. Cooperation was assessed at the time of face mask application (67% N_2O in oxygen [6 L/min fresh gas flow]) followed by a second assessment 30 s later when halothane (0.5%) was added (3).

Taste acceptability was evaluated on a four-point scale (accepted readily, accepted with grimace, accepted with verbal complaint, rejected entirely); a score of 1–3 was considered satisfactory.

A sample size of 306 (102 patients per dose) provided 97% power at a one-sided α of 0.05 to detect a 20% to 25% difference in sedation scores between two doses. The planned enrollment was 369 patients (123 per dose) to allow for an expected unevaluable rate of approximately 20%. Homogeneity across treatment groups for demographic and baseline characteristics was analyzed with the χ^2 test or the Cochran-Mantel-Haenszel test for categorical variables and with analysis of variance for continuous variables. Efficacy variables were analyzed with the Cochran-Mantel-Haenszel statistic, adjusted for age group and baseline value, to test for association between treatment group and response (sedation and anxiolysis). The time to recovery was analyzed by regimen with the Kaplan-Meier survival method. Efficacy data were analyzed by two categories: 1) the intent-to-treat cohort included all patients who were randomized, ingested any amount of oral midazolam syrup, and had

at least one postbaseline assessment; and 2) the standard population cohort consisted of all patients who had at least one postbaseline sedation assessment, underwent mask induction, completed the operation, and recovered in the PACU.

Results

Four-hundred-five patients were enrolled; 8 did not receive the study medication, leaving 397 subjects who fulfilled the criteria for the intent-to-treat analysis and 350 for standard analysis. Demographic characteristics were similar across the three dose groups (Table 1).

Overall, 97% of patients achieved satisfactory sedation (score ≥3) after treatment (Table 2). The difference between the 0.25 and 1.0 mg/kg dosage for all three age groups combined was significant ($P < 0.01$); there was no difference between the 0.5 and 1.0 mg/kg groups or between the 0.5 and 0.25 mg/kg groups. Of the 191 subjects with satisfactory baseline scores, 99% maintained satisfactory scores; of the 206 patients with unsatisfactory baseline scores, 95.1% achieved satisfactory scores. The youngest group was more anxious at baseline than the other two groups ($P < 0.01$). The distribution of maximal sedation in all patients by dose and treatment group is presented in Table 2; two patients reached the maximal level of sedation (asleep). The percentage of patients with unsatisfactory sedation at baseline who achieved satisfactory sedation within 10 min was similar across the three dosage groups (70.1%–78.6%); 91.7% achieved satisfactory sedation between 10 and 20 min. Satisfactory sedation was maintained in >90% of patients for up to 45 min.

After study medication, 97.5% of subjects achieved a satisfactory anxiolytic response (score ≥3). Of the 153 patients with unsatisfactory baseline anxiety scores, 96.1% achieved satisfactory scores. The youngest group had significantly more unsatisfactory sedation scores at baseline than the other two groups ($P < 0.01$). Of the 241 patients with satisfactory baseline scores, 98.7% maintained satisfactory scores. The onset of anxiolysis was nearly identical to the onset of sedation; i.e., 80.4% of patients with unsatisfactory baseline scores developed satisfactory anxiolysis within 10 min after midazolam, and 94.1% developed satisfactory anxiolysis from 10 to 20 min; six patients continued to demonstrate anxiety 30 min after premedication. There was a positive association between dose and onset of anxiolysis ($P = 0.01$); a larger proportion of children achieved satisfactory anxiolysis within 10 min at the higher doses (Fig. 1); >90% maintained satisfactory anxiolysis for up to 45 min.

Cooperation at separation from parents was satisfactory in 88.2% of subjects; no differences were noted between doses. Eighty-two percent demonstrated satisfactory separation within 10 min, 85.8% demonstrated satisfactory separation when separation was attempted from 11 to 20 min after premedication, and 96.4% did so when separation was within 21–30 min. Of the 151 subjects with an unsatisfactory baseline anxiety rating, 84.8% achieved a satisfactory separation response.

Cooperation scores for face-mask acceptance showed an overall satisfactory rate of 86.4%. Of those subjects with unsatisfactory baseline anxiety scores, 81.0% achieved satisfactory cooperation scores with N_2O induction; 90.9% of patients with a satisfactory baseline anxiety score retained satisfactory scores. The incidence of satisfactory scores with the addition of halothane was 84% overall; there was no difference between treatment groups. Overall satisfactory cooperation with face-mask acceptance was found in 80.6% of patients exposed to N_2O from 11 to 20 min after premedication; this increased to 88.8% at 21–30 min. Similar proportions were found for the introduction of halothane, but there was a significant association between regimens and response when adjusted for baseline anxiety scores ($P = 0.03$).

The formulation was accepted by 95.2% of children: 51.9% readily, 26.7% with facial grimace, and 16.4% with verbal complaint; 4.8% rejected the medication entirely. The proportion of patients who accepted the taste was less in the youngest group ($P < 0.01$) compared with the older groups.

The median time to recover to a Steward score of 6 in the PACU was 30 min for all three regimens (Table 3). There was considerable patient-to-patient variability in recovery time. Two patients had prolonged recovery; one received 1.0 mg/kg (total, 15 mg), whereas another received 1.5 mg/kg, in violation of the protocol. Even if we controlled for only patients who ingested the entire dose at the maximum dose per kilogram, i.e., only patients who received exactly 0.25, 0.5, or 1.0 mg/kg, then there still was no relationship between dose and time in the PACU. There was a positive correlation between age and duration of PACU stay ($P = 0.01$, Pearson correlation); the older groups took longer to reach a Steward score of 6 than did the youngest group.

Adverse events were recorded for three time periods (Table 4). The proportion of subjects experiencing an adverse event was slightly larger in the 1.0 mg/kg group. No child experienced respiratory complications before induction; two experienced nausea and three vomited before induction. Changes in blood pressure, heart rate, or respiratory rate after midazolam were quite variable. In some children, there was an increase in blood pressure, heart rate, and respiratory rate over time, whereas in others there was an initial increase in vital signs followed by a decrease. It is unclear to what extent the magnitude and variability of the changes in vital signs were related to children crying or otherwise being upset by the procedure, as distinguished from a direct effect of midazolam.

Table 1. Patient Demographics

Variable	Dose of oral midazolam		
	0.25 mg/kg	0.5 mg/kg	1.0 mg/kg
Overall n	132	132	133
Age (yr) (range)	4.5 ± 3.6 (0.5–15.3)	4.7 ± 3.8 (0.5–14.8)	4.6 ± 3.9 (0.5–15.0)
Weight (kg) (range)	19.4 ± 11.7 (6.4–71.1)	20.2 ± 13.0 (6.8–74)	20.0 ± 13.7 (7.0–76.8)
Duration of surgery, min (range)	62.2 ± 49.5 (5–445)	53.5 ± 45 (6–223)	56.8 ± 42 (5–311)
Procedures (n)			
Dental/dermatology/endoscopy	8	8	11
General surgery/gynecology/multiple services	24	21	30
Neurosurgery/other	1	1	2
Ophthalmology	14	5	7
Orthopedic	4	12	8
Otorhinolaryngology	52	53	50
Plastic	5	8	4
Thoracic	0	0	1
Urologic	24	24	20

This includes all intent-to-treat patients (n = 397). Values are mean ± SD or n.

Table 2. Maximum Sedation Scores Within 30 Minutes of Baseline (n = 397)

Age group	Response	0.25 mg/kg	0.5 mg/kg	1.0 mg/kg
0.5 to <2 yr	Agitated	1	1	0
	Upset/wary	2	1	0
	Relaxed	36	36	33
	Drowsy	8	11	17
	Asleep	1	0	0
2 to <6 yr	Agitated	0	0	0
	Upset/wary	5	0	0
	Relaxed	33	22	23
	Drowsy	5	16	18
	Asleep	0	0	1
6 to <16 yr	Agitated	0	1	0
	Upset/wary	1	0	0
	Relaxed	30	28	26
	Drowsy	10	16	15
	Asleep	0	0	0
Overall	Agitated	1	2	0
	Upset/wary	8	1	0
	Relaxed	99	86	82
	Drowsy	23	43	50
	Asleep	1	0	1

Discussion

Investigators studying the use of oral midazolam as a preanesthetic medication have reported doses of 0.5 to 1.0 mg/kg to achieve satisfactory sedation and anxiolysis in most patients (2,3,7–11). However, these studies used extemporaneous preparations in which the IV midazolam formulation was combined with a variety of components (2,3). Midazolam normally exists in an equilibrium of both an open- and a closed-ring structure, the proportion of which is pH dependent. At lower pH values, there is a greater proportion of drug in the open-ring configuration. Because only the closed-ring configuration is lipophilic and physiologically active, bioavailability is sensitive to changes in pH (4). Therefore, the combination of the IV midazolam formulation with any "home made" diluent could alter both the absorption rate and the bioavailability.

This study design was based on published dose-response data (2,3,7–11,23), the bioavailability data that had been developed at the time of the study design, and the need to develop adequate safety data to satisfy labeling requirements (12). The efficacy of oral midazolam in children had been previously established in other placebo-controlled trials, but the safety and dose response of a standard commercially available preparation had not (3,9,10,13,24,25). This study was designed with an active control, anticipating that the smallest dose (0.25 mg/kg) would have a large fraction of patients achieve a less than desired response. Double that dose (0.5 mg/kg) was expected

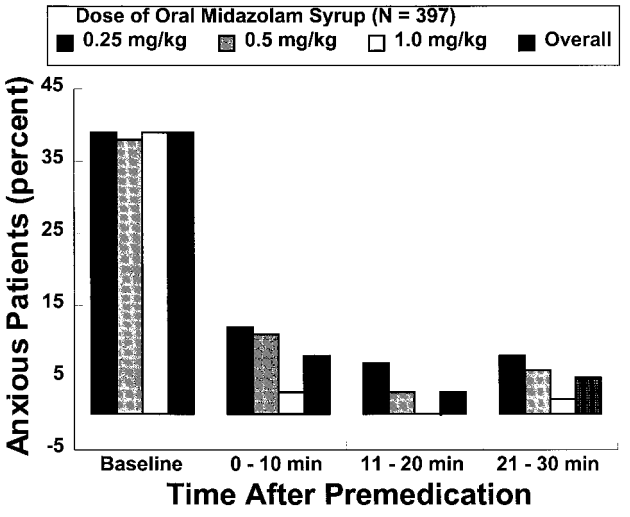

Figure 1. Percentage of patients exhibiting anxiety from baseline to time after oral midazolam. There was a positive association between dose and onset of anxiolysis ($P = 0.01$); a larger proportion of children achieved satisfactory anxiolysis within 10 min at the higher doses.

to place most patients in the desired range, and quadrupling the dose (1.0 mg/kg) was expected to place some patients in the excessively sedated category. The study was not designed to control for surgical procedure or the use of additional anesthetic medications, to more closely reflect common anesthesia practices.

The results of this study were unexpected; i.e., the very smallest dose (0.25 mg/kg) was equally as effective as the two higher doses. Although there was a statistically significant relationship between dose and time of onset for both sedation and anxiolysis, this difference is probably not clinically important. A concurrent trial found that the bioavailability of the commercial preparation was approximately 36%, substantially larger than the anticipated bioavailability on which the dose range for this trial was selected (26) (Reed et al., personal communication, 2001). In retrospect, it would have been better had we had a fourth group that received 0.125 mg/kg as our active control dose. Our results demonstrate the pitfalls of clinical study design that result from incomplete pharmacokinetic information. The pharmacokinetic study with the commercial preparation demonstrated linearity in oral midazolam absorption independent of age or dose (Reed et al., personal communication, 2001).

Notwithstanding the unexpected efficacy of the 0.25 mg/kg dose, our findings demonstrate a high success rate in terms of sedation and anxiolysis, especially in the subpopulation of patients who were anxious at baseline. However, the cooperation scores for acceptance of the face mask were lower, suggesting that some children did not maintain a satisfactory response when stressed. Our findings are consistent with those of other investigators, who used the commercially prepared oral midazolam syrup and found a strong association between plasma concentrations and sedation scores (26).

There was no relationship between midazolam dose and length of stay in the PACU when the entire cohort was evaluated and when the data were weight normalized (i.e., only patients who actually received and ingested 0.25, 0.5, or 1.0 mg/kg with a maximum weight of 20 kg for the 1 mg/kg dose and 40 kg for the 0.5 mg/kg dose). There was wide patient-to-patient variability, which probably reflects other confounding variables, such as the surgical procedure, anesthetic, pain upon awakening, and the need for other sedating medications. Because medications administered after anesthetic induction and surgical procedure were not controlled, these observations probably reflect those that would be observed in the overall pediatric population undergoing elective surgical procedures. There was a significant relationship between patient age and duration of PACU stay. The observation that younger patients recovered more rapidly may reflect a true pharmacodynamic difference, because there was no correlation between duration of procedure and duration of PACU stay, nor was there a relationship between time from premedication, duration of surgery, and duration of PACU stay (27). Several studies have suggested such an inverse relationship between dose sedation response and age (28,29).

This study demonstrated a wide safety profile after oral midazolam, because no patient developed clinically important desaturation before the induction of anesthesia, despite a fourfold difference in dose. Our observations are consistent with other controlled trials of midazolam administered as the only sedating medication (2,9,11,26). In this study, there were five patients who experienced nausea or vomiting before mask induction; these events may have been related to the drug or to the patient's response to ingesting something he or she did not want; i.e., it is difficult to separate a true pharmacodynamic effect from the psychologic response of a child. Although there were no adverse respiratory events before induction, there were several severe adverse respiratory events during induction and maintenance and in the PACU that might have been related to the concomitant administration of midazolam, anesthetic medications, opioids, the surgical procedure itself, and the response of the patient to the constellation of these factors in the perioperative period. These observations emphasize the importance of drug-drug interactions and the need for careful observation of all children who receive combinations of sedating/anesthetic medications (30,31). Also, it must be understood that this study involved a highly selected population of patients, the vast majority of whom were ASA class I or II; this study excluded patients with serious underlying medical conditions. The responses and the potential for adverse

Table 3. Time to Steward Postanesthesia Care Unit (PACU) Score of 6 for all Intent-to-Treat Subjects[a]

Variable	0.25 mg/kg (n = 132)	0.5 mg/kg (n = 132)	1.0 mg/kg (n = 133)	Overall (n = 397)
Recovery time, min	30.3 ± 17.3[b] (5–75)	33.0 ± 18.6[b] (3–90)	35.7 ± 20.3[b] (9–100)	33.0 ± 18.9 (3–100)

Values are mean ± SD (range).
[a] Two patients were believed to have prolonged recovery; one received 1.0 mg/kg and the other received 1.5 mg/kg, in violation of the protocol.
[b] The median recovery time was 30 min in all three treatment groups.

Table 4. Number of Subjects (%) with Adverse Events by Time Period

Adverse event	Regimen	Patients in regimen (n)	Before induction		Anesthesia		PACU		After PACU discharge		Total events	
			n	%	n	%	n	%	n	%	n	%
Nausea	0.25 mg/kg	132	0		0		0		6	4.5		
	0.50 mg/kg	132	0		0		0		2	1.5		
	1.00 mg/kg	133	2	1.5	0		0		5	3.8		
	Overall	397	2	0.5	0		0		13	3.3	15	3.8
Emesis	0.25 mg/kg	132	1	0.8	1	0.8	1	0.8	8	6.1		
	0.50 mg/kg	132	1	0.8	0		2	1.5	3	2.3		
	1.00 mg/kg	133	1	0.8	0		2	1.5	12	9.0		
	Overall	397	3	0.8	1	0.3	5	1.3	23	5.8	32	8.0
Respiratory disorders[a]	0.25 mg/kg	132	0		2	1.5	3	2.3	0			
	0.50 mg/kg	132	0		1	0.8	6	4.5	0			
	1.00 mg/kg	133	1	0.8[b]	5	3.8	5	3.8	1	0.8		
	Overall	397	1	0.3	8	2.0	14	3.5	1	0.3	24	6.0

Before induction = time of premedication to just before induction; Anesthesia = induction until leaving the operating room; PACU = from time of arrival until discharge from the postanesthesia care unit; After PACU discharge = after discharge from the PACU.
[a] Respiratory disorders includes hypoxia, laryngospasm, respiratory depression, airway obstruction, upper airway congestion, hiccups, and coughing.
[b] Upper airway obstruction occurred with initiation of N_2O for the induction of general anesthesia.

respiratory events of higher-risk patients are likely to be different.

Although slightly more than half of the patients readily ingested the commercially prepared midazolam syrup, the remainder grimaced, expressed verbal complaint, or rejected the syrup completely. The youngest age group of patients had the highest rejection rate and also demonstrated the greatest degree of baseline anxiety; this observation probably reflects the developmental age of these patients and the difficulty of gaining their cooperation in swallowing something that they did not wish to swallow.

In summary, the data demonstrate that the commercially prepared oral midazolam formulation is rapidly absorbed, with the majority of patients demonstrating a satisfactory degree of sedation and anxiolysis within 10 minutes of consumption, with a larger percentage at 11–20 minutes. Satisfactory sedation and anxiolysis seems to last for up to 40–45 minutes. The commercial preparation of oral midazolam syrup is effective in doses as small as 0.25 mg/kg, with little advantage gained by doubling or quadrupling the dose. Oral midazolam syrup up to a dose of 1.0 mg/kg (maximum, 20 mg), when not combined with other sedating medications, seems to have minimal effects on hemoglobin-oxygen saturation in healthy patients cared for in a highly supervised environment. This study also highlights the importance of administering standard commercial preparations of drugs to children. Few of the extensive available data suggest that 0.25 mg/kg of oral midazolam would be effective as a preoperative sedative. When evaluating studies of noncommercial, nonstandard oral drug preparations, care must be taken in interpreting prescribing information because there may not be consistent bioavailability; this could then result in inconsistent patient responses.

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