Anesthesiology
78:51–55, 1993

J. B. Lippincott Company, Philadelphia

Midazolam Enhances Anterograde but not Retrograde Amnesia in Pediatric Patients

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Background: **Midazolam sedation has been shown to diminish recall of one to four cards shown prior to induction of general anesthesia in pediatric patients. This promising but limited finding prompted us to investigate the effect of midazolam sedation on retrograde and anterograde recall and recognition in children scheduled for elective surgery.**

Methods: **Forty patients aged 4–10 yr were randomized using a double-blind study design to receive either 0.2 mg/kg intranasal midazolam or 0.2 ml/5 kg placebo (distilled water) using a Devilbiss #286 atomizer. To assess postoperative memory of preoperative events, recall and recognition tasks were performed using a series of picture cards designed for this purpose. Retrograde amnesia was measured by postoperative recall and recognition of cards shown prior to midazolam/placebo administration, and anterograde amnesia was measured by postoperative recall and recognition of cards shown during the interval between midazolam/placebo administration and induction of general anesthesia.**

Results: **Compared to placebo, the midazolam group experienced a significant postoperative reduction in ability to both recall ($P < .003$) and recognize ($P < .001$) cards shown subsequent to midazolam/placebo administration (anterograde amnesia). In distinction, there was no difference between groups in postoperative ability to recall or recognize cards shown prior to midazolam/placebo administration (retrograde amnesia).**

Conclusions: **These results support and extend the inference that midazolam diminishes anterograde recall. In addition, our findings indicate that midazolam diminishes anterograde recognition, thereby providing partial anterograde amnesia without affecting retrograde memory in pediatric patients.**

(Key words: Anesthesia: pediatric. Hypnotics: midazolam. Memory: anterograde amnesia, retrograde amnesia. Premedication: midazolam, intranasal.)

CHILDREN'S behavior can be adversely affected by memory of stressful perioperative experiences. Accordingly, most anesthesiologists find it desirable to administer a premedication that produces amnesia to these events. The ideal amnestic would inhibit recall and recognition of events that occur subsequent to the drug's administration without affecting memory of events that occurred prior to its administration.

Midazolam, administered as a premedicant by various routes (intramuscular,[1,2] rectal,[3,4] intranasal,[5,6] oral,[7] or sublingual[8]), has been described to produce tranquil and calm sedation, reduce separation anxiety from parents, and facilitate induction of anesthesia without significantly prolonging recovery. A number of studies[1,7,9–11] have shown that benzodiazepines diminish recall to a few pictures shown prior to induction of general anesthesia in pediatric patients. The extent of this amnesia, whether to recall antecedent events (retrograde amnesia) or to recall from the period of time subsequent to drug administration (anterograde amnesia) has not been rigorously quantified in children. Neither has the effect of benzodiazepines on either retrograde or anterograde recognition been measured.

Intranasal midazolam can be easily administered,[5,6] and plasma midazolam concentrations required for sedation in children are rapidly achieved.[12] Accordingly, we chose to evaluate aerosolized intranasal midazolam for its effect on both retrograde and anterograde memory loss in children utilizing two memory tasks, recall and recognition, both recommended modes of sampling memory phenomenon in children.[13]

Methods and Materials

Forty children, aged 4–10 yr, ASA physical status I and II, patients undergoing elective procedures re-

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Received from the Long Island College Hospital, Ambulatory Surgical Unit, Brooklyn, New York. Accepted for publication October 2, 1992. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 25–30, 1991.

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quiring general anesthesia for less than 2 h were randomly assigned to one of two treatment groups. Institutional Review Board approval as well as written informed parental consent were obtained. The study was blinded to patients, parents, anesthesiologists administering anesthesia, and nursing staff conducting the observations. The midazolam group received 0.2 mg/kg midazolam (drug concentration 5 mg/ml), and the placebo group received 0.2 ml/5 kg of distilled water. Both agents were administered intranasally using equal volumes from a Devilbiss #286 atomizer (Somerset, PA). General anesthesia was standardized and consisted of 70% N_2O and 30% O_2, with variable concentrations of halothane and muscle relaxant administered as needed subsequent to induction with halothane, N_2O, and O_2 *via* mask.

To assess postoperative memory of preoperative events, memory testing was performed using a series of picture cards as described by Snodgrass and Vanderwart.[14] Sets of 16 black-and-white picture cards were matched for difficulty according to categories that included food, clothes, school supplies, transportation, animals, body parts, toys, and furniture. Preoperatively, baseline memory testing including both recall and recognition tasks was conducted as follows: in the presence of the subject's parents, each child was shown 16 picture cards and was asked to verbally identify each item to ensure correct identification. After a 5-min inspection period the cards were collected and the child was asked to recall the content of cards he/she had been shown (subsequently referred to as recall). The child was then shown 32 cards, including the 16 cards previously seen and 16 novel distractor cards, and asked to recognize cards previously seen (subsequently referred to as recognition). The order of card presentation was varied between subjects to randomize primacy (impact) and recency (order) effects. A minimum score of five correct responses in either memory task was required prior to placebo/midazolam administration to qualify for continued study. Recall was again tested with a new set of 16 cards 10 min after the child received either drug or placebo. Activity level was simultaneously assessed on a 1–5 ordinal scale (1 = asleep, 2 = drowsy, 3 = calm, 4 = anxious, 5 = agitated). The child was then transported to the operating room. Two hours after the child arrived in the post anesthesia care unit, memory testing was again conducted by asking the child to verbally recall any of the cards shown preoperatively and recognize both sets of preoperative cards from among 32 new distractor cards. No postoperative pain medication was administered.

Interval data were analyzed by analysis of covariance and *t* tests, categorical variables by chi-square, and nonparametric variables by Mann-Whitney-U tests. Statistical significance was accepted at $P < .05$.

Results

Two patients were excluded from the study because of baseline memory scores lower than 5 (one from each group). One patient was excluded from the midazolam group when duration of operation exceeded 2 h, and three patients did not complete postoperative memory testing because of clerical inefficiencies unrelated to the study (two in the midazolam group and one in the placebo group). Data analysis included the remaining 34 patients. There were no statistically significant differences between treatment groups with respect to age, gender distribution, activity level 10 min subsequent to midazolam/placebo administration, average duration of operation, maximal halothane concentration used, or time to awakening after discontinuation of anesthetic agents (table 1). Both groups accepted the premedication and separated from their parents equally satisfactorily. No laryngospasm, hemoglobin desaturation, or other complications were reported. Types of surgery performed included ear, nose, throat (75%); general (17%); and ophthalmologic (8%).

Preoperative memory results are presented in table 2. Baseline and post drug/placebo measures were corrected for age and false-positives, and post drug/placebo was also corrected for activity level and baseline scores.

Table 1. Demographic and Independent Variables

	Placebo	Midazolam
n	15	19
Age (yr)	6.8 ± 1.3	6.6 ± 2.0
Sex		
Male	5	8
Female	10	11
Activity level 10 min post midazolam/placebo	3.25 (2–5)	3.03 (2–4)*
Average duration of operation (min)	25 ± 15	27.9 ± 18†
Maximal halothane concentration (%)	2.1% ± 0.78	1.9% ± 0.87†
Time to awakening (min)	10.2 ± 9.3	9.9 ± 8.3†

* Median (range).

† Mean ± SD.

Table 2. Baseline and Immediate Post-Drug Memory Testing*

	Placebo (n = 15)	Midazolam (n = 19)	P
Baseline			
Recall			
Observed	9.00 ± 0.62	7.74 ± 0.51	
Adjusted	8.95	7.77	.09†
Recognition			
Observed	16.00 ± 0.00	14.95 ± 0.47	
Adjusted	15.64	15.13	.38†
Immediate post drug			
Recall			
Observed	6.21 ± 0.55	1.56 ± 0.50	
Adjusted	6.36	1.43	<.001‡

* Mean ± SE.

† Adjusted by analysis of covariance to correct for the effects of age and false positive responses.

‡ Adjusted by analysis of covariance to correct for the effects of age, baseline score, activity level, and false positive response.

All postoperative memory data underwent analysis of covariance by group, controlling for age, baseline memory, performance activity level, and the number of false-positive picture cards identified. When assessing postoperative memory of events occurring subsequent to drug/placebo administration (anterograde effect), we found significant differences between the two groups in both recall and recognition (table 3): the midazolam group recalled an average of 1.78 cards compared to the placebo group's recall of 4.01 cards ($P < .003$) and recognized an average of 6.64 cards, compared to placebo recognition of 14.39 cards ($P < .001$). There was no difference between groups in ability to remember cards that were shown prior to drug administration (retrograde effect, table 4): the midazolam group recalled an average of 6.81 cards compared to 5.84 cards in the placebo group ($P = .386$) and recognized an average of 15.29 *versus* 15.22 for the placebo group ($P = .878$).

Table 3. Anterograde Recall and Recognition: Midazolam *versus* Placebo*

	Placebo (n = 15)	Midazolam (n = 19)	P
Recall			
Observed	3.93 ± 0.55	1.84 ± 0.51	
Adjusted	4.01	1.78	<.003†
Recognition			
Observed	13.73 ± 0.53	7.16 ± 1.23	
Adjusted	14.39	6.64	<.001†

* Mean ± SE.

† Adjusted by analysis of covariance to correct for the effects of age, baseline score, activity level, and false positive results.

Table 4. Retrograde Recall and Recognition: Midazolam *versus* Placebo*

	Placebo (n = 15)	Midazolam (n = 19)	P
Recall			
Observed	6.27 ± 0.78	6.47 ± 0.77	
Adjusted	5.84	6.81	.39†
Recognition			
Observed	15.53 ± 0.17	15.05 ± 0.47	
Adjusted	15.22	15.29	.88†

* Mean ± SE.

† Adjusted by analysis of covariance to correct for the effects of age, baseline score, activity level, and false positive results.

Discussion

Premedication that provides sedation, encourages cooperation, and renders children amnestic to perioperative experiences is quite desirable. Interfering with memory of information stored prior to sedation could be detrimental. Accordingly, an ideal amnestic should selectively affect only memory experiences related to the period immediately prior to and during surgery. The amnestic properties of the benzodiazepines have been well studied in the adult population. Benzodiazepines impair acquisition of new information with no effect on retention or retrieval of previously stored information.[15-17] In addition, and consonant with our finding that differences in memory scores were not affected when adjusted for activity level, there is strong evidence that the amnesia produced is specific and separate from the sedative action of benzodiazepines.[16] Midazolam, in particular, is reported to provide significant amnesia[18-22] and has gained in popularity as a premedicant because of its rapid onset of action and relatively short duration with an elimination half-life of less than 3 h.

The effect of midazolam on memory in the pediatric population has not been studied extensively. Feld *et al.*,[7] in their evaluation of oral midazolam as a premedicant, and Taylor *et al.*,[1] in comparing intramuscular midazolam to other sedative hypnotics, showed their subjects a single picture card preoperatively and found that their midazolam groups had significantly less recall of the object depicted compared to other treatment groups. Additional studies have found children to be amnestic to one or two objects more in benzodiazepine groups compared to placebo or non-ben-

zodiazepine groups.[9-11] The effect of benzodiazepines on either retrograde or anterograde recognition has not been measured previously in children. Accordingly, we chose to evaluate aerosolized intranasal midazolam for its effect on both retrograde and anterograde memory loss in children utilizing two memory tasks, recall and recognition, both recommended modes of sampling memory phenomenon in children.[13]

Memory is difficult to evaluate in children because they frequently make inaccurate responses independent of memory function[23] and because developmental influences vary with age. Children's central nervous systems undergo rapid changes that cause underlying or baseline differences in higher cognitive functions. These differences affect the way children perform various memory tasks. Age related influences on memory were evident in our data—children 6 yr old and younger had a higher number of false-positive answers on recognition tests and lower scores overall. In addition, subjects receiving placebo also experienced within-group decline in recall (37%) prior to surgery. We speculate that this may be due to increased fatigue and/or increased anxiety that interfered with learning independently of retention. Accordingly, scores were covaried for subject's age, baseline performance, and activity level.

Although the psychobehavioral literature describes various models of developmental memory phenomenon, our interest in them is limited to the extent that they affect the memory tasks chosen. Recall, both free and cued, permits analysis of a child's storage, retention, and retrieval abilities. The child needs to search through memory to find correct responses. Recall performances improve with age as well as does the development of patterns for memorization or memory strategies (*e.g.*, mnemonics, categorization).# Recall is also the more common task that anesthesiologists use to test for awareness that may have occurred perioperatively. It is, however, more subject to opportunities for intrusion or distraction, which may elicit incorrect answers and guesses. Because of these concerns, all the memory data were covaried for false-positive responses to eliminate the effect of guessing. Recognition tasks are less difficult to perform and are less sensitive to developmental differences. Both recall and recognition utilize episodic memory, which is a component of long-term memory that consists of memory from personal experiences within specific contexts, the primary area that benzodiazepines inhibit.[17] Recognition as well as recall depend on whether perceived material is familiar.[24]

Another limitation of memory testing in children is the paucity of age-based norms for comparison of data. Accordingly, we used normative data to control for level of difficulty of stimuli and insure approximate comparability across repeated tests. We utilized picture cards described by Snodgrass and Vanderwart[14] that were evenly mixed according to categories, familiarity, name agreement, and simplicity. In addition, we included baseline pretreatment measurements with multiple (16–32) stimuli at each testing interval and varied the distractor cards for each set of memory tests so that subjects could direct their attention toward the tested materials.

Ghoneim *et al.*[25] have compared the quality of assessment of memory in the anesthesia and psychopharmacology literature and reported that, in general, anesthesiology tends to be lacking compared to psychopharmacology in the variety of methods of memory assessment employed, use of pictures rather than words for memory tests, and reliance upon questions that test recall, as distinct from recognition of perioperative events. The psychopharmacology literature was also found to be more likely to use control or placebo groups, pre- and posttreatment memory measurements, and multiple memory tests with distinct equated stimuli, and more often postulates a relationship between methodology employed and a theoretical model of memory.

When studying the effects of drugs on memory, it is useful to integrate the experimental designs of both cognitive psychologists and clinical pharmacologists. These considerations were integrated into the design of our study to test and/or elaborate previous findings discussed in the anesthesiology literature.[1,7,9-11] This design enabled us to confirm and extend the finding that midazolam significantly reduces children's postoperative ability to recall and recognize cards shown subsequent to midazolam administration without affecting their memory of cards shown prior to sedation.

The authors wish to thank Dr. Reuben Margolies for his counsel on statistical analysis, and Ms. Janine Lagana and Ms. Defarge for their expert technical assistance in preparing this manuscript.

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