Midazolam

Effects on Amnesia and Anxiety in Children

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Background: The minimum time interval between administration of oral midazolam and separation of children from their parents that ensures good anterograde amnesia has not been previously determined. This is of particular importance in a busy operating room setting where schedule delays secondary to midazolam administration may not be tolerated.

Methods: Children (n = 113) undergoing general anesthesia and surgery completed preoperative baseline memory testing using a validated series of picture cards and were randomly assigned to one of three midazolam groups or a control group. Exactly, 5, 10, or 20 min after receiving oral midazolam (0.5 mg/kg) or 15 min after receiving placebo, children were administered a second memory test that used pictures. Anxiety of children was assessed during induction of anesthesia with use of a validated anxiety measurement tool. Postoperatively, recall and recognition for picture cards seen during baseline testing and postintervention testing were assessed.

Results: Postoperatively, recall and recognition of pictures presented to patients after drug administration (anterograde amnesia) showed significant group differences ($P = 0.0001$), with recall impaired in the 10- ($P = 0.004$) and 20-min groups ($P = 0.0001$). Similarly, recognition memory was impaired in the 5- ($P = 0.0008$), 10- ($P = 0.0001$) and 20-min ($P = 0.0001$) groups. Significant anxiolytic effects of midazolam were observed as early as 15 ± 4 min after midazolam administration ($P = 0.02$).

Conclusions: Midazolam administered orally produces significant anterograde amnesia when given as early as 10 min before a surgical procedure. (Key words: Benzodiazepines; pediatrics; surgery.)

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EXTREME preoperative anxiety in children may prolong the induction of anesthesia and lead to new-onset postoperative negative psychologic effects, such as nightmares, eating disturbances, and enuresis.[1–3] Preoperative use of midazolam has previously been reported to decrease the incidence of these postoperative negative psychologic outcomes,[4] and midazolam-related amnesia has been suggested as the mediator for this phenomena. That is, the less the child remembers about the perioperative events, the less psychologic trauma he or she will experience. A recent large-scale survey, however, indicated that midazolam is not widely used for young children undergoing anesthesia and surgery.[5] For example, only 25% of all children younger than age 3 are routinely premedicated in the United States.[5] The low frequency with which sedative premedication is used may be a concern because of the adverse outcomes that are associated with high levels of preoperative anxiety.

Many anesthesiologists do not administer preoperative sedatives because of timing and economical issues. For example, the manufacturer of oral midazolam[6] recommends it be administered at least 20 min before surgery. Not infrequently, however, surgical procedures are relocated, surgeons do not arrive on time, and patients show up late for surgery, resulting in a short administration time for an oral sedative. Previous studies that have addressed timing in relation to surgery issues in children have evaluated the onset of anxiolytic effects of midazolam, but not the onset of the amnestic effects of midazolam.[7] As indicated previously herein, however, the

amnestic effects of midazolam may be more important than the anxiolytic effects because amnesia may mediate postoperative negative behavioral changes described in children.

The primary purpose of this investigation was to determine the minimum amount of time necessary for effective anterograde amnesia to develop in children after oral administration of midazolam.

Materials and Methods

Study Design and Subjects

In this double-blind, placebo-controlled, randomized trial, the study population consisted of 131 children, aged 5–10 yr, American Society of Anesthesiologists physical status I or II, undergoing general anesthesia and elective, outpatient surgery scheduled for less than 2 h duration. To avoid potential confounding variables, history of chronic illness, prematurity, or developmental delay excluded subjects from participation in this study. The institutional review board of Yale University approved the protocol, and all parents provided informed written consent.

Eligible patients were randomly assigned to one of four study groups according to a list created from a random-numbers table:

Group 1 received 0.5 mg/kg midazolam (parental formulation, Roche Laboratories, Inc. Nutley, NJ) mixed in 10 mg/kg oral acetaminophen (McNeil-PPC, Inc. Fort Washington, PA) orally and underwent memory testing exactly 5 min after receiving the mixture.

Group 2 received 0.5 mg/kg midazolam (parental formulation, Roche Laboratories, Inc.) mixed in 10 mg/kg oral acetaminophen (McNeil-PPC, Inc.) orally and underwent memory testing exactly 10 min after receiving the mixture.

Group 3 received 0.5 mg/kg midazolam (parental formulation, Roche Laboratories, Inc.) mixed in 10 mg/kg oral acetaminophen (McNeil-PPC, Inc.) orally and underwent memory testing exactly 20 min after receiving the mixture.

Group 4 received 10 mg/kg oral acetaminophen (McNeil-PPC, Inc.) and underwent memory testing exactly 15 min after receiving acetaminophen.

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Outcomes and Instruments

The primary outcome was children's recall and recognition memory for items of the memory test presented after receiving the intervention medication. A secondary outcome was the anxiety of the child during induction of anesthesia. Detailed psychometric data regarding the following behavioral instruments were reported previously by our study group.[4,8] A psychologist functioned as the assessor and administered the various observational tools.

Temperament and Anxiety.

- State Trait Anxiety Inventory for Children (STAI-C).[9] This self-report anxiety instrument contains two, separate 20-item subscales that measure trait (baseline) and state (situational) anxiety.
- Modified Yale Preoperative Anxiety Scale (mYPAS).[10] This observational measure of anxiety contains 27 items in five categories (activity, emotional expressivity, state of arousal, vocalization, and use of parents) that indicate preoperative anxiety in children.
- EASI Scale of Child Temperament (EASI).[11] This instrument includes 20 items in four categories: emotionality, activity, sociability, and impulsivity.

Memory. To assess postoperative memory of preoperative events, memory testing was performed using a series of picture cards, as described by Snodgrass and Vanderwart.[12] Detailed psychometric data regarding this instrument and its use with children are reported elsewhere.[12] Six sets of 12 black-and-white picture cards were used, matched for name agreement, image agreement, familiarity, and visual complexity according to categories that included food, clothes, school supplies, transportation, animals, body parts, toys, and furniture.‡‡ Each child was asked to verbally identify 12 picture cards as they were presented and to study the cards for a period of 2 min (fig. 1A). After 1 min, the child was again asked to verbally name each picture. After the 2-min inspection period, the cards were collected and the child was asked to recall the content of cards he or she was just shown (recall test). The child was then immediately presented with 24 cards, the 12 cards previously seen and 12 new distractor cards, and asked to point to the cards previously seen (recognition test). The order of memory-card presentation varied between subjects to randomize primacy (impact) and recency (order) effects. It took approximately 5 min to administer the memory testing described (fig. 1A). Therefore, testing time must be added to intervention time when considering the influence of the intervention.
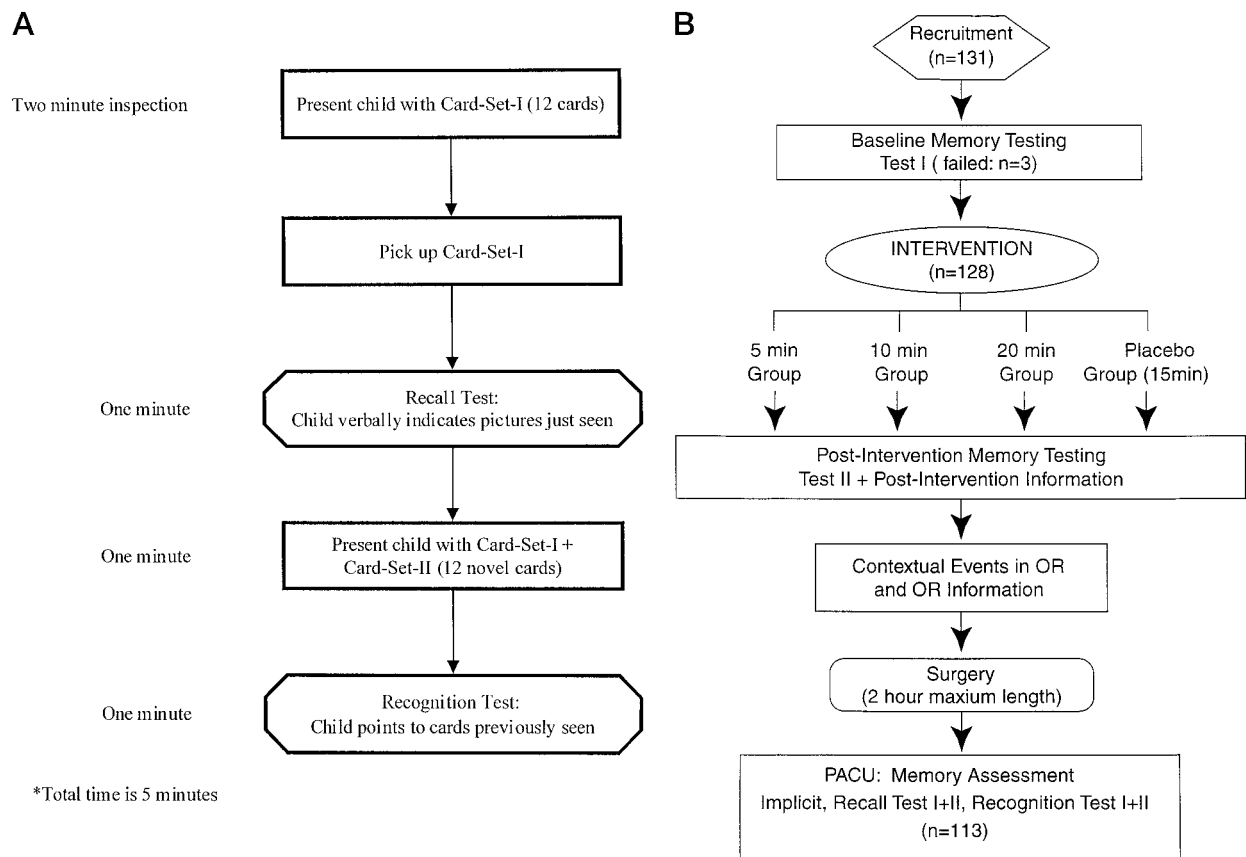
A

Two minute inspection → Present child with Card-Set-I (12 cards)

↓

Pick up Card-Set-I

↓

One minute → Recall Test:
Child verbally indicates pictures just seen

↓

One minute → Present child with Card-Set-I +
Card-Set-II (12 novel cards)

↓

One minute → Recognition Test:
Child points to cards previously seen

*Total time is 5 minutes

B

Recruitment
(n=131)

↓

Baseline Memory Testing
Test I (failed: n=3)

↓

INTERVENTION
(n=128)

5 min Group | 10 min Group | 20 min Group | Placebo Group (15min)

↓

Post-Intervention Memory Testing
Test II + Post-Intervention Information

↓

Contextual Events in OR
and OR Information

↓

Surgery
(2 hour maxium length)

↓

PACU: Memory Assessment
Implicit, Recall Test I+II, Recognition Test I+II
(n=113)

Fig. 1. (A) Memory-test procedure for baseline and postintervention memory-test sessions. (B) Study protocol.

Study Protocol

After recruitment and informed written consent was obtained, baseline information, including demographic data, temperament of the child (EASI), and trait anxiety of the child (STAI-C) were obtained.

Preintervention. While the parent completed the baseline information, the child was underwent the baseline memory test session. Five correct responses for either the recall or the recognition test were necessary for participation in the study. Next, the child was randomized to one of the four study groups and given the administered intervention medication (fig. 1B).

Postintervention. Exactly 5, 10, or 20 min after receiving midazolam or 15 min after receiving placebo, all children underwent a second memory test session. This postintervention memory test was identical in format to the baseline memory test session (fig. 1A), except that 12 new test cards and 12 new distractor cards were used during the session.

Operating room. All children were to be taken to the operating room (OR) immediately after the second mem-

ory test session (fig. 1B). Because of OR procedural issues, however, some children were delayed, and therefore, anxiety assessment during induction of anesthesia sometimes occurred later than planned. Information about the timing of induction of anesthesia in relation to administration of the intervention is presented in the Anterograde Effects section herein. After the child entered the OR, a member of the research team pointed to a large picture sticker on his or her shirt and directed the child's attention to it. The child was then asked to name the picture and to repeat the name a second time. The child was not told to remember the information.

Anxiety of the child was assessed at entry to the OR and at introduction of the anesthesia mask (mYPAS). Anesthesia was induced in all subjects using a controlled oxygen-nitrous-oxide–sevoflurane technique. After induction, an intravenous cannula was inserted and 0.1 mg/kg intravenous vecuronium was administered to facilitate intubation. Anesthesia was maintained with oxygen–nitrous oxide and isoflurane. Intravenous fentanyl (1–3 μg/kg) was administered based on the decision of the individual attending

anesthesiologist. Anesthetic management for children undergoing myringotomies consisted of mask induction with no intravenous cannula and no tracheal intubation. Regional anesthesia was not performed on any of the subjects in the study and drugs such as ketamine or droperidol were not used.

Postanesthesia care unit. Incidence of adverse effects and time to discharge were recorded. Before discharge, with the child awake and alert, a third and last memory session was undergone (fig. 1B). Children were asked about contextual events that took place in the OR before and during induction of anesthesia, including the presentation of the sticker by the assessor, and the last thing they remembered before "going to sleep." Specific questions were asked about placement of the pulse oximeter and electrocardiography leads ("do you remember the doctor putting something on your finger or chest?"). Children were then asked to recall all of the picture cards they had seen since arriving to the surgery center, including the two sets seen during baseline testing and the two sets seen during postintervention testing, for a total of four sets of cards. After recall, the four sets seen previously and the 12 new distractor cards were shown to assess recognition memory.

Statistical Analysis

The sample size is based on a previous investigation that involved nasal midazolam and amnesia in children.[13] This was calculated (SamplePower, version 1.0; SPSS, Inc., Chicago, IL) for one-way analysis of variance with four levels and a moderate effect size (f) of 0.35, a power of 0.85, and an α of 0.05. A minimum of 25 cases/cell were needed for a total of 100 cases for the study. Because the age of a child is an important determinant of memory function, subjects were matched using a yoked design based on age. For example, the first 5-yr-old child recruited was randomized to one of the four study groups, the second 5-yr-old child recruited was randomly allocated to one of the three remaining study groups, the third 5-yr-old child recruited was randomly allocated to one of the two remaining study groups, and so forth. This ensured equal distribution of ages in the four study groups, while maintaining strict randomization.

Demographic data, including family characteristics and measures of clinical recovery, were analyzed using analysis of variance and the chi-square test, as appropriate. Changes in preoperative anxiety were analyzed using repeated-measures analysis of variance, with treatment group as the grouping factor and time as the repeated measure. Normally distributed data are presented as the mean $\pm$ SD and skewed data as median and interquartile range (25–75%). Skewed data were analyzed using nonparametric tests. As the distribution of memory scores violated the assumption of normality, memory performance was evaluated using the Kruskal-Wallace H or Mann–Whitney U test, as appropriate. Comparisons were considered to be significant if $P < 0.05$.

Results

A total of 131 children were approached for recruitment for this study. One hundred and thirteen subjects completed postanesthesia care unit (PACU) memory assessment (n = 113). Thus, 18 subjects were excluded because of failure in the initial memory screening test (n = 3), surgery that lasted more than 2 h (n = 7), timing issues in memory testing (n = 7), and unexpected hospital admission (n = 1; fig. 1B). There were no significant differences between the placebo and intervention groups regarding demographic and family characteristics (table 1).

Memory

Baseline Testing (First Session). As the distribution of memory scores violated the assumption of normality, memory performance was evaluated using the Kruskal-Wallace H test. Baseline measures of recall and recognition memory were comparable in the four intervention groups (table 2). Furthermore, there were no group differences in the number of distractor cards (cards not previously seen) chosen during recognition.

Postintervention Testing (Second Session). In the memory test after intervention administration, there were significant group differences in recall ($P = 0.0001$) and recognition scores ($P = 0.0001$; table 2). Compared with memory performance in the placebo group, recognition and recall memory was impaired in both the 10-min ($P = 0.002$) and the 20-min ($P = 0.0001$) groups but not in the 5-min group ($P = $ NS).

Postanesthesia Care Unit Testing (Third Session). *Retrograde effects.*

Recall. Recall in the PACU of pictures presented at baseline (before intervention) showed significant group differences ($P = 0.003$), where recall was better in the 10-min ($P = 0.002$) and 20-min ($P = 0.0001$) groups, as compared with the placebo group. In contrast, the 5-min group did not differ from the placebo group ($P = $ NS). A comparison of recall in the PACU for pictures across the two preoperative test sessions revealed that children

Table 1. Baseline and Perioperative Variables

Characteristic	5-min Group (n = 25)	10-min Group (n = 30)	20-min Group (n = 25)	Placebo Group (n = 33)	P Value
Age (yr)	7.6 ± 1.5	7.3 ± 1.8	7.6 ± 1.8	7.4 ± 1.6	NS
Gender (%)					
Male	64	56	48	76	NS
Female	36	44	52	24	
Child temperament					
Emotionality	10.6 ± 4.6	11.9 ± 3.9	11.5 ± 3.9	10.7 ± 3.7	NS
Activity	14.3 ± 3.4	15.2 ± 4.8	14.7 ± 4.7	14.9 ± 3.9	NS
Sociability	18.1 ± 3.2	19.1 ± 2.4	17.8 ± 2.7	19.3 ± 2.8	NS
Impulsivity	11.8 ± 3.2	12.1 ± 4.4	12.8 ± 3.9	11.6 ± 4.4	NS
Child's Trait Anxiety*	33.9 ± 8.9	35.3 ± 4.8	33.6 ± 6.6	36.9 ± 9.7	NS
Hollingshead Index	27.7 ± 13.5	25.3 ± 14.5	21.1 ± 6.8	20.9 ± 10.1	NS
Type of surgery (%)					
Ear–nose–throat	40	48	28	29	NS
General–minor	32	34	44	37	NS
Duration of surgery (min)†	54 (26–77)	60 (24–75)	61 (33–98)	59 (47–80)	NS
Time to discharge (min)†	110 (87–125)	120 (85–150)	120 (87–152)	110 (76–133)	NS

Unless otherwise indicated, data are presented as mean ± SD.

*As assessed by the State Trait Anxiety Inventory for Children.

†Median (25–75%).

NS = not significant.

in the placebo and the 5-min groups recalled significantly more pictures from the subsequent, more recent test session than from the first, baseline test session (25 *vs.* 12.5%, *P* = 0.01; table 2). Therefore, a recency effect may be present for the 5-min and placebo groups (see Discussion).

Recognition. Recognition in the PACU of test and distractor pictures presented at the baseline test session (before intervention) showed no group differences (*P* = NS; table 2).

Anterograde effects.

Recall. Recall in the PACU of pictures presented after the intervention showed significant group differences (*P* = 0.0001). Specifically, recall was impaired in the 10-min (*P* = 0.004) and 20-min groups (*P* = 0.0001), as compared with the placebo group (table 2). The 5-min

Table 2. Recall and Recognition Memory Scores in Each of the Four Groups

| Memory Assessment | Group | | | | P Value |
	5-min	10-min	20-min	Placebo	
Preoperative memory performance					
Baseline, % correct					
Recall	58.3 (50–67)	58.3 (50–67)	66.7 (58–75)	66.7 (58–75)	NS
Recognition	100 (92–100)	100 (92–100)	100 (83–100)	100 (92–100)	NS
Postintervention, % correct					
Recall	50.0 (37–63)	33.3 (16–33)*	16.7 (2–16)†	58.3 (37–67)	0.0001
Recognition	100 (85–100)	83.3 (50–100)*	58.3 (41–81)†	100 (91–100)	0.0001
Postoperative memory performance					
Retrograde memory, %					
Recall	12.5 (8–33)	25 (8–42)*	33 (16–50)†	12.5 (0–25)	0.003
Recognition	91.6 (79–100)	91.6 (81–100)	91.6 (83–100)	100 (92–100)	NS
Anterograde memory, %					
Recall	25.0 (0–33)	8 (0–29)‡	0 (0–0)†	25.0 (8–33)	0.0001
Recognition	83.3 (67–96)§	70.8 (42–92)†	41.6 (4–75)†	91.6 (91.6–100)	0.0001

Data are presented as median (25–75%).

All significant group differences are between the treatment groups and placebo group.

Post hoc comparisons by Mann–Whitney U tests (* *P* = 0.002, † *P* = 0.0001, ‡ *P* = 0.004, § *P* = 0.0008).

NS = not significant.

Table 3. Implicit Recall of Contextual Events

Contextual Events Questions	5-min Group	10-min Group	20-min Group	Placebo Group	P Value
Operating room information*					
Did the doctor put something on your finger?†	39.1#	35.7**	16.7††	71.9	0.000
Did the doctor put something on your chest?‡	40.9	25.9#	27.3**	61.3	0.02
What was on the doctor's shirt?§	33.3	9.5	21.4	34.6	NS
Last memory‖					
Smell of mask	20	16	8	40#	0.01
Blowing up a balloon	4	0	0	6	NS
Playing with the "memory game"	20	13	20	12	NS
Unclear, nothing, no answer	20	10	16	6	NS
Took medication	4	7	8	3	NS
Kissing parent	0	0	8	6	NS
Watching TV	0	0	4	0	NS

* Percent of correct responses.

† Refers to placement of pulse oximeter probe.

‡ Refers to placement of ECG leads.

§ Refers to picture sticker.

‖ Percent responses.

$P \leq 0.02$.

** $P \leq 0.005$.

†† $P \leq 0.0001$.

ECG = electrocardiography; NS = not significant.

group was not different compared with the placebo group (P = NS). Because the test procedure necessitates a 2-min inspection time before recall (fig. 1A), the earliest outcome we evaluated (5-min group) occurred 7 min after intervention (*i.e.*, 5 + 2 min). Similarly, 2 min should be added for the actual time that recall was evaluated for the other groups.

Recognition. There were also significant group differences for recognition in the PACU of pictures presented after the intervention (P = 0.0001). Compared with the placebo group, recognition of test cards was impaired in the 5- (P = 0.0008), 10- (P = 0.0001), and 20-min (P = 0.0001) groups (table 2). Recognition memory was assessed after recall, and so the time elapse between administration of the intervention and start of recognition evaluation was 4 min (2-min inspection + 1-min recall + 1 min to present test and distractor cards). Therefore, the earliest influence we evaluated (5-min group) was 9 min after the intervention. (*i.e.*, 5 + 4 min).

Anxiety Assessment and Contextual Events

The times from intervention to entrance to the OR and undergoing induction of anesthesia for each of the four treatment groups were 15 ± 4 (5-min group), 21 ± 7 (10 min group), 33 ± 10 (20-min group), and 24 ± 10 min (placebo group). Thus, evaluation of memory for contextual events and anxiety levels during induction of

anesthesia occurred at least 10 min after the intervention because of the time necessary to administer and complete the memory-test session, transportation time to the OR, and unexpected OR delays.

Compared with children in the placebo group, fewer children in the 5- (P = 0.015), 10- (P = 0.005), and 20-min (P = 0.0001) groups recalled placement of the pulse oximeter probe (table 3). Similarly, compared with children in the placebo group, fewer children in the 10- (P = 0.015) and 20-min (P = 0.007) groups recalled placement of the electrocardiography leads. Also, significantly more children in the placebo group reported the smell of the anesthesia mask as their last memory, as compared with children in the 5-, 10-, and 20-min groups (P = 0.01).

Analyses of changes in anxiety levels across three preoperative time points (*i.e.*, holding, entrance to the OR, and introduction of the anesthesia mask) showed a significant group-by-time interaction [F (6,212) = 2.3, P = 0.035]. Further analyses showed that anxiety in the four groups differed during entrance to the OR [F (3,107) = 4.00, P = 0.01] and at introduction of the anesthesia mask [F (3,107) = 5.04, P = 0.003]. Compared with the placebo group, anxiety at entrance to the OR was lower in the 5- (P = 0.02), 10- (P = 0.009), and 20-min groups (P = 0.003). Furthermore, compared with the placebo group, anxiety at introduction of the anesthesia mask

Table 4. Anxiety Scores across Time

	Group				
Time Point	5-min	10-min	20-min	Placebo	P Value
Holding area	27 ± 7	31 ± 10	28 ± 8	29 ± 9	NS
Entrance to OR	30 ± 12*	30 ± 13†	27 ± 8†	33 ± 11	0.01
Introduction of anesthesia mask	33 ± 14†	34 ± 15†	27 ± 10‡	45 ± 18	0.003

As measured by the modified Yale Preoperative Anxiety Scale. Data are mean ± SD.

* $P \leq 0.05$, as compared with the placebo group.

† $P \leq 0.01$, as compared with the placebo group.

‡ $P \leq 0.001$, as compared with the placebo group.

NS = not significant; OR = operating room.

was lower in the 5- ($P = 0.01$), 10- ($P = 0.01$), and 20-min ($P = 0.001$) groups (table 4). That is, midazolam administration at any of the three time points reported previously herein resulted in lower levels of anxiety in the OR.

Discussion

This study was undertaken to establish the minimum amount of time necessary for effective anterograde amnesia to develop in children after administration of oral midazolam. We found that recognition memory was impaired as early as 10 min after oral midazolam administration, and recall was impaired as early as 13 min after oral midazolam administration. Therefore, there is significant evidence to support administration of oral midazolam in children, even when only 10 min are available until planned surgery. Significant anxiolytic effects of midazolam can be observed as early as 15 ± 4 min after midazolam intake.

Determining the minimum amount of time needed for sedative premedication to take effect is particularly important in a busy OR setting. Not infrequently, procedures are relocated, surgeons may be late, and patients may not arrive until 15 min before scheduled surgery time. Therefore, it is very important to know the minimum time necessary for the sedative premedication to take effect before bringing a child into the OR. Previously, this issue was addressed only with regard to the onset of effective anxiolysis. For example, Levine *et al.*[7] suggested that the minimum time interval between administration of midazolam and separation of children from their parents is 10 min. Because amnesia is an important outcome that may effect the postoperative behavior of the child, we thought that the minimum time interval for administration of oral midazolam should also be evaluated, with amnesia as the outcome of interest.

Preoperative use of midazolam has previously been reported by our study group to decrease the incidence of postoperative negative behavioral changes during the first postoperative week.[4] It should be emphasized, however, that no data indicate the reason for this phenomena; however, we have hypothesized that midazolam-related amnesia is the cause. Additional studies are needed to establish the relation between midazolam-related amnesia and postoperative behavioral changes. One could argue that postoperative negative behavioral changes are a normal function that helps the child to adapt to the new situation after surgery. With this theory, blocking behavioral changes is not advisable because it would interfere with the adaptive response. We believe that many changes in behavior can be either adaptive or maladaptive, depending on how they are interpreted by the child and the child's parents. For many parents, behavioral changes postsurgery are worrisome. Although parents may understand that the changes are related to the surgery, they do not always see this as adaptive, and, indeed, these behavioral changes may be problematic for child and parent alike. We do not advocate blocking postoperative behavioral changes altogether, rather we propose that the blunted memory is used to keep the stress response in the adaptive range. Moreover, an acute traumatic psychologic event may result in posttraumatic stress disorder (PTSD), a phenomenon that may lead to significant negative long-term effects.[14] We are not proposing that all children should receive midazolam preoperatively to block perioperative memory, and we are not suggesting that posttraumatic stress disorder will develop in all children after surgery. However, we suggest that midazolam may play a major role in keeping the postoperative behavioral stress response in the adaptive range for many children.

Anterograde amnesia as a result of benzodiazepine use is a robust phenomenon that is well-described in the sci-

entific literature.[13,15–19] Previous investigations that involved adults have shown that midazolam-induced amnesia is associated with a dose–response curve.[18] Twersky *et al.*[13] compared a group of children premedicated using nasal midazolam with a group of children premedicated using nasal placebo. The midazolam group experienced a significant postoperative reduction in ability to recall and recognize cards shown subsequent to nasal midazolam administration (anterograde amnesia). The question regarding the minimum time interval between receiving the nasal midazolam and memory testing, however, was not within the scope of that study. Also, it is important to emphasize that most children in the United States are premedicated preoperatively with use of oral midazolam, and most children think the nasal route to be extremely unpleasant.[5,20] In a similar investigation, Payne *et al.*[19] demonstrated that midazolam administered orally resulted in a 60% incidence of amnesia, as compared with a 16% amnesia in a control group. Payne, *et al.*[19] also reported that the induction process was remembered by 50% of the children who received midazolam, compared with 81% of the control group. Again, the timing factor was not addressed by these investigators. Other studies have also addressed the issue of amnesia and administration of midazolam in children, but the issue of timing has never been addressed to the best of our knowledge until the current study.[21,22]

Of particular interest is the observation concerning retrograde recall amnesia. We found that recall in the PACU for the first session cards was better in the 10- and 20-min groups, as compared with the 5-min and placebo groups, and that children in the placebo and 5-min groups recalled significantly more pictures from the second, more recent test session than from the first test session. One explanation for this phenomenon is that a recency effect may exist. *Recency phenomena* can be defined simply as better remembering for the last event in a series, as compared with the first event in the series.[23] For children in the 10- and 20-min groups, the last event that occurred before becoming amnestic was the first test session. For children in the 5-min and placebo groups, the second test session was the last event before becoming amnesic. We should emphasize, however, that recency effects are highly influenced by interruptions, and, because of the time elapsed, recency effects may not entirely explain these retrograde amnesia findings.

Our finding that recognition memory was impaired as early as 10 min after oral midazolam administration should be put in the context of previously published kinetic data regarding this drug. Payne *et al.*[24] administered 0.45 mg/kg oral midazolam to a group of children undergoing surgery and measured serum concentrations in these children up to 5 h postadministration. The investigators found that the time to peak serum level after oral administration was 53 ± 21 min. They also report, however, that midazolam achieved 57% of its peak concentration as early as 15 min after oral administration (33.6 ± 20.2 *vs.* 59.5 ± 23.5 ng/ml). These findings should be interpreted with caution because the therapeutic serum levels of benzodiazepines are subject to wide interpersonal variation.[25] In adult patients, however, reliable sedation is reported to exist with a midazolam serum concentration of 40 ng/ml upward.[26] Therefore, considering that, in the current study, we used a dose that was higher by 10% than that used by Payne *et al.*[24] and considering that the plasma concentration reported by Payne *et al.* at 15 min was close to 40 ng/ml,[24] our findings of sedation within 15 after oral administration of midazolam can be anchored to previously published kinetic data.

Several methodological issues related to this study must be addressed. First, because of timing issues, we were unable to determine the minimal amount of time needed between administration of oral midazolam and the presence of effective anxiolysis. For example, the 5-min group underwent induction 15 ± 4 min after receiving the oral midazolam, at which time the group exhibited significant anxiolysis. However, anxiolysis may have started earlier. This timing issue had no effect on our findings regarding onset of amnesia because memory timing was carefully controlled. Second, we did not address the issue of postoperative behavioral changes as they relate to the amount of amnesia manifested by each child. It would have been beneficial to assess whether children who were more amnestic exhibited less behavioral changes than children who were less amnestic. This issue is important and should be addressed in future studies. Third, the response of various patient groups to the amnestic properties of midazolam may vary based on the procedure they are about to undergo. That is, for children undergoing surgery for the first time, amnesia may be of great benefit. In contrast, children who undergo repeated procedures, such as burn dressing changes, and who receive midazolam repeatedly may be frightened because they will not remember what happen to them previously and, therefore, when brought for dressing changes the second time, they cannot draw on past experience. This later phenomena needs to be further investigated.

In conclusion, this investigation showed that anterograde amnesia exists as early as 10 min after administra-

tion of oral midazolam. Anesthesiologists who have a limited time interval between administration of midazolam and induction of anesthesia should be aware of this information and modify their practice based on these findings.

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