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Effects of Age and Emotionality on the Effectiveness of Midazolam Administered Preoperatively to Children

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Background: **Multiple studies document the beneficial effect of midazolam on preoperative anxiety in children. Many clinicians report, however, that some children may in fact not benefit from the administration of this drug.**

Methods: **After screening for relevant exclusion criteria, children undergoing surgery were enrolled in the study (n = 262) and received 0.5 mg/kg oral midazolam at 20–40 min before induction of anesthesia. Personality instruments were administered to all children, and anxiety levels were evaluated before and after administration of midazolam as well as during induction of anesthesia. Blood was drawn during the induction process and later analyzed for midazolam levels. *A priori* definitions of responders and nonresponders to midazolam were established using a multidisciplinary task force, videotapes of induction, and a validated and reliable anxiety scale, the modified Yale Preoperative Anxiety Scale.**

Results: **While 57% of all children scored at the minimum of the modified Yale Preoperative anxiety scale, 14.1% of children fell in the *a priori* defined group of midazolam nonresponders. Midazolam blood levels (94 ± 41 *vs.* 109 ± 40 ng/ml) and timing between administration of midazolam and induction (28 ± 9 *vs.* 29 ± 8 min) did not differ between midazolam responders and nonresponders. In contrast, midazolam nonresponders were younger (4.2 ± 2.3 *vs.* 5.9 ± 2.0 yr), more anxious preoperatively (49.7 ± 22.9 *vs.* 38.3 ± 19.1), and higher in emotionality (13.6 ± 3.6 *vs.* 11.3 ± 3.8) as compared with responders ($P < 0.05$).**

Conclusions: **Although midazolam is an effective anxiolytic for most children, 14.1% of children still exhibit extreme distress. This subgroup is younger, more emotional, and more anxious at baseline. Future studies are needed to determine the best strategy to treat these children.**

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ALTHOUGH the exact prevalence of preoperative anxiety in children is difficult to estimate because of measurement difficulties and developmental variation, up to 50% of children undergoing surgery are reported to exhibit significant manifestations of anxiety in the preoperative period.[1] Both psychological and pharmacologic interventions are available to treat preoperative anxiety in children. Among the preoperative pharmacologic interventions, midazolam is the most commonly used drug in the United States.[2,3] Indeed, a recent large-scale national survey study indicated that when a preoperative sedative is given to children, midazolam is the choice in more than 90% of cases and that midazolam is mostly administered before surgery orally at a dose of 0.5 mg/kg.[3] Although midazolam has been reported to provide effective preoperative anxiolysis,[4–6] many clinicians are aware that some children still exhibit extreme distress despite premedication. Indeed, several previous investigations have indicated that administration of midazolam does not result in "satisfactory" results in some children. For example, in a recent large-scale randomized controlled trial, it was found that although 97.5% of children receiving midazolam "achieve satisfactory anxiolytic response," only 86% had "satisfactory anxiety ratings at face mask application."[7] It is important to note, however, that anxiety in this study was measured using a four-point scale with no validity or reliability data reported. Hence, it is unclear what "satisfactory anxiolytic response" means. Finely *et al.*[8] published a study that was specifically aimed at examining the particular issue of children who are poor responders to preoperative midazolam. Unfortunately, this investigation was hindered by methodologic limitations such as lack of adequate study power and lack of data regarding midazolam levels in the blood.

Based on a comprehensive review of the literature, we submit that identifying and characterizing children who are nonresponders to preoperative midazolam requires careful study design. Such a study should enroll an appropriate number of subjects, use a clinically valid oral midazolam dose, use a valid and reliable anxiety rating instrument, and measure midazolam levels in the blood. Confounding variables such as parental presence during induction, the use of other sedatives, and the use of any drugs that affect cytochrome P-450 should be eliminated. The anesthetic induction protocol must also be controlled. Valid personality instruments should be used in an effort to characterize children who do not respond to midazolam, and multivariate analysis should be performed to account for the individual contribution of

potential predictors. Last, an *a priori* data-driven and clinically based definition of children who are nonresponders to preoperative midazolam should be developed.

In a study designed according to these criteria, we sought to examine the incidence of children who are preoperatively sedated with midazolam but still exhibit signs of extreme anxiety and distress. As a secondary outcome, we aim to identify the characteristics of these children.

Materials and Methods

Outpatient children aged 2–10 yr, with American Society of Anesthesiologists physical status I–III, who were scheduled to undergo general anesthesia and elective surgery were considered for enrollment in this cross-sectional controlled study. Patients were excluded from participation if they had a history of prematurity or chronic illness and a history of developmental delay. Children with any gastrointestinal disorders, children taking either cytochrome P-450 inhibitors (*e.g.*, grapefruit juice, erythromycin) or cytochrome P-450 inducers (*e.g.*, phenobarbital) were not enrolled in the study. A repeated-measures design was used in which each subject's behavior was evaluated throughout the perioperative period. The Yale Institutional Review Board (New Haven, Connecticut) reviewed and approved the experimental protocol of the study; all parents provided written informed consent, and all children provided assent (when appropriate). The use of parental presence during induction of anesthesia was not allowed during this study.

Baseline and Outcome Measures

All the behavioral measures were administered by trained research personnel who had significant background in behavioral sciences. Our laboratory, the Center for the Advancement of Perioperative Health, has standardized protocols for training of all research personnel (details available from corresponding author). Briefly, all new personnel have to follow experienced staff until deemed trained as assessed by determination of interrater and intrarater reliability. New personnel have to rate 10 videotaped inductions of anesthesia and achieve interrater and intrarater reliability of at least 95% agreement on the rating of instruments such as the modified Yale Preoperative Anxiety Scale (mYPAS). Thereafter, all personnel have to be tested every 6 months to assure that these reliability parameters are maintained.

EASI Instrument of Child Temperament (Child). The EASI Instrument of Child Temperament is a standardized tool that assesses the various aspects of temperament in children and is used widely in the literature.[9,10] This instrument includes 20 items in four behavioral categories: Emotionality, Activity, Sociability, and Impulsivity. A parent is presented with individual patterns of behaviors and responses to daily events and is asked to rate the child on a five-point scale. The score ranges from 5 to 25 for each category, with higher scores indicating higher baseline Emotionality, Activity, Sociability, or Impulsivity. The instrument has good validity when compared with other measures of temperament for preschool children. Test–retest reliability of the EASI temperament tool was high when mothers rated their preschool children on adjacent months.[9,10]

Yale Preoperative Anxiety Scale (Child). This observational measure of preoperative anxiety was developed and validated in previous investigations.[11,12] The mYPAS consists of 27 items in five categories of behavior indicating anxiety in young children (Activity, Emotional Expressivity, State of Arousal, and Vocalization). Using κ statistics, all mYPAS categories have been demonstrated to have good to excellent interrater and intraobserver reliability (0.73–0.91), and when validated against other global behavioral measures of anxiety, the mYPAS had good validity ($r = 0.64$). The mYPAS score ranges from 22.5 to 100, with higher scores indicating greater anxiety. Since its development, this scale has been used in multiple investigations (*e.g.*, references 8 and 13–17).

State-Trait Anxiety Inventory (Parent). The State-Trait Anxiety Inventory (STAI) is a widely used self-report anxiety assessment instrument.[18] To date, more than 1,000 studies involving research using the STAI have been published in peer-reviewed literature. The questionnaire contains two separate 20-item, self-report rating scales for measuring trait and state anxiety. Parents respond on a four-point scale; total scores for situational and baseline questions separately range from 20 to 80, with higher scores denoting higher levels of anxiety. Test–retest correlations for the STAI are high, ranging from 0.73 to 0.86. Validity of the instrument was examined in two studies in which the STAI was given under high- and low-stress conditions to large samples of students. The *r* value ranged from 0.83 to 0.94, suggesting very good validity.

Induction Compliance Checklist (Child). The Induction Compliance Checklist (ICC), an observational scale, was developed by our laboratory in a previous investigation.[13] The ICC includes a checklist containing 11 items indicating compliance during induction of anesthesia. The ICC score is the sum of the items checked. A perfect induction, *i.e.*, the child does not exhibit negative behaviors, fear, or anxiety, is scored as 0. Intraclass *r* for this scale ranges between 0.995 and 0.998. Interclass *r* between the two observers is high as well: 0.978.

Miller Behavioral Style Scale (Parent). The Miller Behavioral Style Scale assesses parental coping style through four scenarios of stressful situations.[19,20] This standardized tool was developed for patients undergoing

medical procedures and identifies information seekers (monitors) and information avoiders, and distractors (blunters)/nondistractors. This measure has excellent reliability and validity.

Study Protocol

Recruitment Phase. Subjects were recruited the night before surgery if they did not participate in the preparation program. The program is voluntary and consists of providing information to the children and parents through an orientation tour of the operating room and modeling by child-life specialists. After recruitment, written consent, demographic data, and baseline measures, including temperament (EASI), trait anxiety (STAI), and coping style of the parent (Miller Behavioral Style Scale), were obtained.

Day of Surgery, Preoperative Holding Area. Child and parental state anxiety (STAI) was assessed before administration of midazolam. After the assessment, all children received 0.5 mg/kg oral midazolam (Ranbaxy Inc., Princeton, NJ).

Separation to Operating Room. Children were evaluated upon separation to the operating room (mYPAS). Timing of separation in relation to the administration of midazolam was controlled to be 20–40 min.

Induction of Anesthesia. After all children were brought into the operating room, an Spo_2 probe was placed on child's hand, and a scented anesthesia mask was presented to the child. Oxygen–nitrous oxide was introduced in a ratio of 3:7 l flow for 2 min, and sevoflurane was started at a concentration of 0.5% and then increased every three breaths to a maximum of 6%. If a child became noncompliant during induction, the mask induction was continued as planned with the child restrained. After anesthesia was induced, an intravenous cannula was inserted, and blood for the measurement of midazolam levels was drawn. The behavior of the child during induction was evaluated by an observer using the mYPAS and ICC. The rating was performed at two time points: (1) entering the operating room and (2) introduction of the anesthesia mask to the child.

Plasma Midazolam Analysis

Plasma levels of midazolam and 1-hydroxymidazolam were determined using a modification of high-performance liquid chromatography.[21] Briefly, after addition of internal standard (200 ng alprazolam) to 0.5 or 1.0 ml plasma and solid-phase extraction (C18 RIK-SEPCOL-1 Sep-Column; Peninsula Laboratories, Belmont, CA), the methanol eluant was evaporated, redissolved in mobile phase (55%, pH 4.5, 0.05 M KH_2PO_4 containing 12 ml/l triethylamine; 45% acetonitrile), and injected on the high-performance liquid chromatography system (15 × 0.46 cm, C18 Microsorb column; ultraviolet absorbance detection at 250 nm). Midazolam was determined with an assay-to-assay coefficient of variation of 6.9%. Levels of 1-hydroxymidazolam were determined in a similar manner, using a mobile phase differing only in that 50% methanol was used instead of 45% acetonitrile. Midazolam and 1-hydroxymidazolam were determined with assay-to-assay coefficients of variation of 6.9% and 5.5%, respectively.

Statistical Analyses. Descriptive statistics provide an overview of the relations between the child–parent variables and the anxiety level in the child. Normally distributed data are presented as mean ± SD; skewed data are presented as median and interquartile range [median (25–75%)]. Correlation analyses were used to evaluate relations between children's anxiety at induction and demographic and temperament variables. Given that mYPAS data were positively skewed, nonparametric correlations are presented. Univariate analyses including *t* tests (for continuous variables) and chi-square tests (for dichotomous variables) were used to evaluate differences between responders and nonresponders. Comparisons were considered significant if $P < 0.05$. Follow-up logistic regression was used to identify the independent contribution of potential predictor variables. Data were analyzed with the use of SPSS version 14.0 (SPSS Inc., Chicago, IL). Missing data were replaced with the variable mean of the corresponding group (responder or nonresponder). It is of note that no variable or participant had more than 5% data missing.

Definition of Responders and Nonresponders to Midazolam. For the purpose of this study, we defined an *a priori* minimum mYPAS score above which a child was considered to be exhibiting extreme anxiety and thus a nonresponder to midazolam. The establishment of this mYPAS score was accomplished by assembling a small task force of anesthesiologists, a clinical psychologist, a statistician, a pediatrician, and a developmentalist. The task force examined mYPAS items in each domain, reviewed videotapes of 20 children undergoing induction of anesthesia, and reached agreement regarding the behaviors (items) in each of the four mYPAS domains that were exhibited by nonresponders: in the Activity domain, a score of 3 or higher; in the Vocalizations domain, a score of 4 or higher; in the Emotional Expressivity domain, a score of 3 or higher; and in the Arousal domain, a score of 3 or higher. These items corresponded to an overall mYPAS score of 72.91 or higher. Table 1 lists the mYPAS items; asterisks mark items that had to be observed for a child to be defined as extremely anxious (nonresponder).

To confirm the grouping of children at mYPAS score of 72.91, *t* tests were conducted to validate this grouping against compliance with anesthesia induction. Although there is no question that anxiety and compliance in children are distinct domains, they are closely related. We found that children with mYPAS scores above 72.91 were significantly less compliant during induction than children with mYPAS scores of 72.90 and below (5.17

Table 1. Proportion of Responder and Nonresponder Children Exhibiting Modified Yale Preoperative Anxiety Scale Behaviors

		Responders, % (n = 225)	Nonresponders, % (n = 37)
Domain: Activity			
1	Looking around, curious, playing with toys, reading (or other age-appropriate behavior); moves around holding area/treatment room to get toys or go to parent; may move toward OR equipment	76.3	2.7
2	Not exploring or playing, may look down, may fidget with hands or suck thumb (blanket); may sit close to parent while waiting, or play has a definite manic quality	18.7	2.7
3*	Moving from toy to parent in unfocused manner, non–activity-derived movements, frenetic/frenzied movement or play; squirming, moving on table, may push mask away	4.1	37.8
4*	Actively trying to get away, pushes with feet and arms, may move whole body; in waiting room, running around unfocused, not looking at toys or will not separate from parent	0.9	56.8
Domain: Vocalizations			
1	Reading (nonvocalizing appropriate to activity), asking questions, making comments, babbling, laughing, readily answers questions but may be generally quiet; child too young to talk in social situations or too engrossed in play to respond	76.3	2.7
2	Responding to adults but whispers, "baby talk," only head nodding	9.1	0
3	Quiet, no sounds or responses to adults	11.4	2.7
4*	Whimpering, moaning, groaning, silently crying	2.3	32.4
5*	Crying or may be screaming "no"	0.5	29.7
6*	Crying, screaming loudly, sustained (audible through mask)	0.5	32.4
Domain: Emotional Expressivity			
1	Manifestly happy, smiling, or concentrating on play	74	2.7
2	Neutral, no visible expression on face	17.8	0
3	Worried (sad) to frightened, sad, worried, or tearful eyes	6.8	25
4*	Distressed, crying, extremely upset, may have wide eyes	1.4	72.2
Domain: State of Apparent Arousal			
1	Alert, looks around occasionally, notices/watches anesthesiologist (could be relaxed)	28.6	6.7
2	Withdrawn child sitting still and quiet, may be sucking on thumb or face turned in to adult	55.7	6.7
3*	Vigilant looking quickly all around, may startle to sounds, eyes wide, body tense	11.4	26.7
4*	Panicked whimpering, may be crying or pushing others away, turns away	4.3	53.3

* Designates items that must be present for a child to be categorized as a nonresponder.

OR = operating room.

vs. 0.23; $P = 0.001$). To further clarify the issue, we have compared the frequency of the mYPAS items between responders and nonresponders (table 1).

Results

A total of 262 children ranging in age from 2 to 10 yr participated in this study. Baseline characteristics of the sample including demographics, EASI scores, and STAI state and trait scores are shown in table 2.

Descriptive Data

The distribution of mYPAS scores upon introduction of the anesthesia mask during the induction process is shown in figure 1. Although a majority of children (57.4%) scored at the lowest possible end of the mYPAS scale (22.9), overall scores ranged from 22.9 to 100. Closer examination of the distribution of scores revealed that 14.1% of children fell in the *a priori* defined group of midazolam nonresponders (mYPAS score greater than 72.9). To ensure that differences in blood levels of midazolam and its active metabolite, 1-hydroxymidazolam, did not account for individual differences in children's response to midazolam, blood samples were collected from a subgroup of children. We found that there were no significant differences in midazolam and 1-hydozymidazolam blood levels, or time between midazolam administration and anesthesia induction between responders and nonresponders (table 3). Furthermore, midazolam blood levels and time from midazolam administration to anesthesia induction were not related to child anxiety levels at induction (P = not significant; fig. 2).

Table 2. Demographic Characteristics of Participants (n = 262)

Child's age, mean ± SD (range), yr	5.68 ± 2.46 (2–10)
Child's sex, % male	57.8
Ethnicity, %	
White	79.80
African-American	7.10
Hispanic	1.60
Other	5.30
Child temperament, mean ± SD (range)	
Emotionality	11.57 ± 3.87 (5–25)
Activity	16.34 ± 4.29 (5–25)
Sociability	18.11 ± 2.71 (7–24)
Impulsivity	12.99 ± 4.10 (5–25)
Parent anxiety (STAI) , mean ± SD (range)	
Trait anxiety	38.68 ± 6.11 (27–56)
State anxiety in holding	43.66 ± 11.39 (22–76)

STAI = State-Trait Anxiety Inventory.

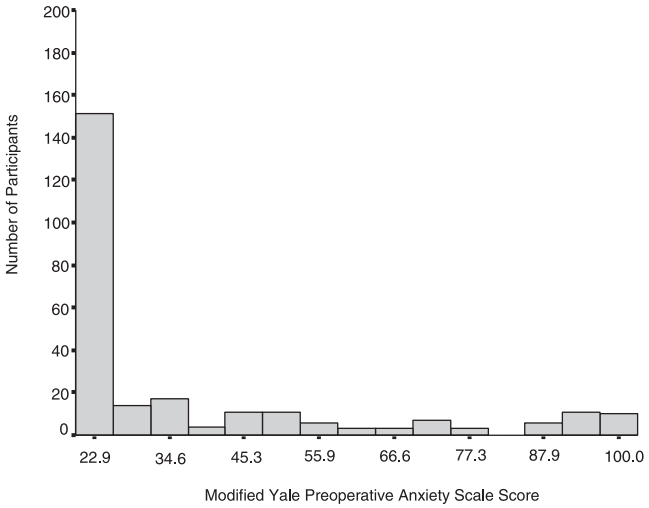

Fig. 1. Distribution of anxiety scores of participants at induction of anesthesia.

There were also no significant correlations between midazolam blood levels and any other variable of interest (EASI subscales, mYPAS, STAI, or ICC).

Correlation analyses were next conducted between anxiety at induction and child age, child anxiety in holding, child temperament (EASI score), and parent anxiety. Child emotionality showed a significant correlation with mYPAS at induction (Spearman rho = 0.174, $P < 0.01$). The correlation between child anxiety in holding and anxiety at induction was also significant (Spearman rho = 0.340, $P < 0.01$), indicating that children who displayed greater anxiety in holding also demonstrated greater anxiety at induction.

Table 3. Variables of Interest for Midazolam Responders (*i.e.*, mYPAS at Induction <72.90) and Nonresponders (*i.e.*, mYPAS at Induction >72.91)

	Responders (n = 225)	Nonresponders (n = 37)	*P* Value
Midazolam level,* mean ± SD, ng/ml	93.6 ± 41.1	108.9 ± 39.3	NS
1-Hydroxymidazolam level, mean ± SD, ng/ml	62.8 ± 28.3	49.4 ± 20.4	NS
Time, mean ± SD, min	28.0 ± 9.0	29.0 ± 8.0	NS
Induction compliance, mean ± SD	0.23 ± 0.59	5.03 ± 2.55	0.001
Child temperament (EASI), mean ± SD			
Emotionality	11.3 ± 3.8	13.6 ± 3.6	0.001
Activity	16.3 ± 4.4	16.5 ± 3.8	NS
Sociability	18.2 ± 2.8	17.8 ± 2.5	NS
Impulsivity	13.1 ± 4.2	12.8 ± 3.8	NS
Attended preadmission visit, %	42.21	44.40	NS
Child age	5.9 ± 2.04	4.25 ± 2.26	0.001
Child anxiety (mYPAS), mean ± SD			
Holding (after midazolam)	38.3 ± 19.1	49.6 ± 22.9	0.002
Parent anxiety (STAI), mean ± SD			
Holding	42.9 ± 11.2	47.5 ± 11.7	NS

* Midazolam levels were collected for subsample (n = 90 responders, n = 18 nonresponders).

mYPAS = modified Yale Preoperative Anxiety Scale (range 22–100); NS = not significant; STAI = State-Trait Anxiety Inventory (range 20–80).

Predictive Data

Univariate Analysis. We found that children who did not respond to midazolam were significantly younger than those who did respond to midazolam ($P = 0.001$; table 3). Indeed, a significantly higher proportion of children younger than 4 yr (24.7%) were categorized as nonresponders, whereas only 8.1% of children older than 4 yr were categorized as such ($P = 0.001$). Distributions of responders and nonresponders by age are shown in figure 3. We also found that children who did not respond to midazolam scored significantly higher on the Emotionality subscale of the EASI than children who responded to midazolam ($P = 0.001$; table 3). Results on the Activity, Sociability, and Impulsivity EASI subscales were not significantly different between groups. Nonresponders in this study were also significantly more anxious in the preoperative holding area than responders ($P = 0.002$). No significant differences on parental state and trait anxiety and participation status in the voluntary preparation program were found between responders and nonresponders.

Multivariate Analyses. Because of the correlation that was found between some of the univariate predictors (age and anxiety), we next conducted a multivariate analysis (table 4). This type of analysis enables us to identify the independent contribution of each of the above univariate predictors (see Univariate Analysis). A logistic regression analysis was performed with group assignment (responder *vs.* nonresponder) as the outcome variable and with child age, child anxiety at preoperative holding, and the EASI subscales as predictors. A test of the model with these six predictors against a constant only model was statistically reliable ($\chi^2(6) = 31.9$, $P < 0.001$), indicating that as a group, these variables reliably distinguish between midazolam responders and nonresponders. Prediction success by the resultant regression equation was excellent, with 85.4% of cases correctly classified by the equation. In terms of importance of individual variables, regression coefficients, Wald χ^2, and odds ratios in this model are shown in table 4. According to the Wald criteria, Emotionality and child age reliably and independently predicted responder group membership.

Discussion

Under the conditions of this study, we found that 14.1% of children who received 0.5 mg/kg oral midazolam exhibited extreme anxiety and distress during induction of anesthesia. When comparing this nonresponsive group with all other children, we found that midazolam

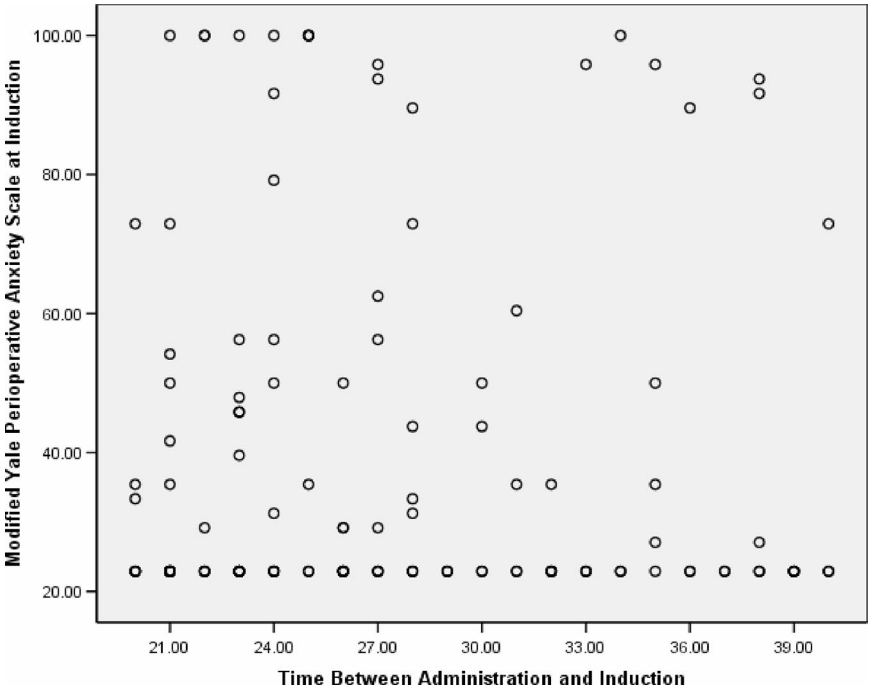

Fig. 2. Children's anxiety at anesthesia induction as a function of time exposure to midazolam.

blood levels and 1-hydroxymidazolam blood levels, as well as time elapsed between midazolam administration and induction of anesthesia, did not differ between the two groups and did not predict the anxiety of the child during induction. In contrast, multivariate analysis indicated that children in the nonresponsive group were younger and scored higher on the Emotionality aspect of the EASI. The results highlight the importance of clinicians considering these two variables when administering preoperative midazolam to children.

Based on the results of this current study, clinicians should be aware that children who are younger than 4 yr and highly emotional may not respond well to 0.5 mg/kg oral midazolam. Increasing the dose of oral midazolam to 0.75 mg/kg in this selected group of nonresponders may lead to lower anxiety scores, although a randomized controlled trial is need to confirm the effectiveness of this suggestion. Further, given that a combination of pharmacologic and nonpharmacologic interventions have been found to be the most effective in other areas of anxiety reduction,[22] clinicians may consider incorporating nonpharmacologic methods of anxiety reduction, such as distraction and relaxation into their care of these children.

Age effects on dosage requirements have been previously discussed in the anesthesiology literature.[23] For example, Taylor and Lerman[24] described an age-related minimum alveolar concentration phenomena, noting increased requirements of volitional anesthetics in young children. A similar phenomenon has been described with propofol.[25] The findings of this article certainly are in line with these previous studies. Also, Nishiyama *et al.*[26] reported an age-related phenomena in adults where decreasing doses were necessary with increasing age. The intravenous doses of midazolam found to be optimal in this study were 0.08, 0.06, and 0.04 mg/kg for patients aged 20–39, 40–59, and 60–79 yr, respectively. Findings regarding age effects on midazolam doses in children

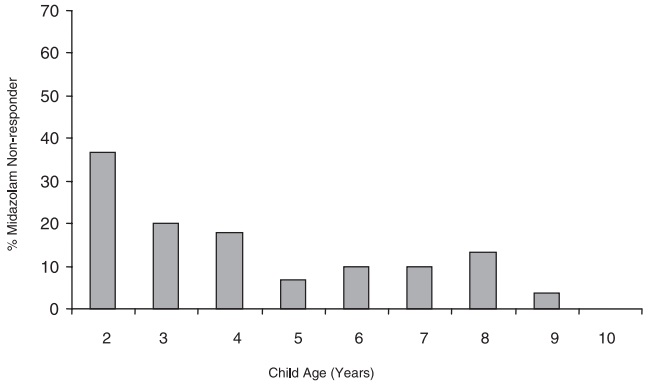

Fig. 3. Proportion of children categorized as midazolam nonresponder by child age.

Table 4. Logistic Regression Results: Responder *versus* Nonresponder as the Outcome Variable

Variable	β	SE	Wald χ^2	Odds Ratio	95% CI	*P* Value
Child temperament						
Emotionality	0.209	0.06	11.89	1.23	1.09–1.39	0.001
Activity	0.007	0.06	0.012	1.01	0.89–1.14	NS
Sociability	0.037	0.08	0.216	1.04	0.89–1.21	NS
Impulsivity	−0.102	0.07	2.5	0.903	0.80–1.03	NS
Child age, yr	−0.324	0.1	11.428	0.724	0.60–0.87	0.001
Child anxiety (mYPAS)	0.016	0.01	3.231	1.02	0.99–1.03	NS

CI = confidence interval; mYPAS = modified Yale Preoperative Anxiety Scale; NS = not significant.

have been equivocal. Indeed, several previous clinical studies on the effectiveness of oral midazolam in children did not identify significant age effects.[7,27] For example, a recent large-scale (397 children) multicenter study found that the effectiveness of midazolam was not age dependent and that a dose of 0.25 mg/kg was as effective as higher doses. It is notable that the differences in findings between those of the previous large-scale study and those of the current study were likely due to measurement issues. Indeed, this previous investigation used a five-point sedation scale for the assessment of the outcome that has not been psychometrically validated. In contrast, the current investigation used an assessment instrument that has received thorough psychometric validation and has been shown to be sensitive, valid, and reliable. The use of such an instrument may well have contributed to the ability to detect age-dependent responses to midazolam in children.

At this point, it is important to highlight that age effects on midazolam response were found in the absence of differences in plasma midazolam or 1-hydroxymidazolam levels. As such, the mechanism of this effect is interesting. Given the absence of plasma drug level differences, it is likely that the age-related differences in anxiolysis are related to pharmacodynamic rather than pharmacokinetic variables. It is well established that midazolam exerts its anxiolytic effects by acting on γ-aminobutyric acid type A receptors.[28] Although this receptor complex has been well studied in adults, there are still many questions regarding the ontogeny of γ-aminobutyric acid type A expression, distribution, and coupling.[29–31] A recent review article in the *New England Journal of Medicine* called for more research exploring postnatal developmental of receptor systems that impact the drug response of children in various age groups.[32]

In addition to the age-effect findings, the finding that children's response to midazolam varies by child temperament, specifically emotionality, is also interesting. Although it might be assumed that younger children are more emotional, thus accounting for this effect, it is important to note that child age was not correlated with emotionality and, further, that emotionality and age independently contributed to prediction of responder group. As such, children's level of emotionality was independently related to their response to midazolam (and was not related to plasma drug levels). The finding that emotionality is the temperament characteristic of importance in this sample is particularly interesting in light of the previously discussed findings of Finley *et al.*[8] These authors reported an association between higher impulsivity and higher anxiety at induction in premedicated children, but found no relation with emotionality. Although Finley *et al.* used the same measures as the current study, it is notable that their sample size (n = 20 for the midazolam group) was small and that Finley *et al.* did not measure or control for midazolam blood levels. The finding that the emotionality subscale of the EASI differentiated between responders and nonresponders is of particular utility to clinicians. This subscale consists of five short items that pertain to the how easily the child cries or gets upset, whether the child has a short temper or is easily frightened, and how easygoing the child is. Although replication of these findings is warranted, the emotionality subscale of the EASI could be shortened in future investigations and thus provide immediate information to the anesthesiologist about children's predicted response to midazolam.

Although there is no question that oral midazolam at a dose of 0.5 mg/kg is an effective preoperative anxiolytic for the typical child who undergoes surgery, we seem to have identified a subgroup of children who do not benefit from this dose of midazolam. This finding is strengthened by several methodologic aspects of the current study. First, we examined the effectiveness of 0.5 mg/kg oral midazolam because this dose and route of administration are the most commonly recommended and used among US anesthesiologists when treating children.[2] Second, we chose a time interval of 20–40 min based on common clinical practice and studies that have examined the onset of action of midazolam.[2] To ensure that midazolam blood levels were not responsible for differences between responders and nonresponders, we measured plasma midazolam and 1-hydroxymidazolam levels in a subgroup of the study patients. Notably, there was no difference between the responders and nonresponders in drug or drug metabolite blood levels.

In addition to the strengths of this study, methodologic limitations should be mentioned. Most notably, although the mYPAS has received extensive psychometric evaluation over the past 10 yr, the dichotomous scoring method presented here has not been used elsewhere. Although this algorithm was based on an *a priori* decision of a multidisciplinary task force, it is in need of further empirical validation. In addition, it is notable that this study included only those children who had not participated in a preoperative preparation program and thus may not generalize to those children who have been a part of such a program. However, it is equally important to note that, although common in children's hospitals, preoperative preparation is not standard care in community hospitals.[33] Further, studies indicate that such preoperative preparation programs do not reduce the anxiety in children during induction of anesthesia.[34]

In conclusion, we found that 14.1% of all children receiving oral midazolam before surgery still exhibit extreme anxiety and lack of compliance during induction of anesthesia. These nonresponder children are younger in age and highly emotional. Based on the findings of this investigation, it is necessary that clinicians develop alternative approaches to children who are nonresponders.

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