Comparison of the Effectiveness of Oral Diazepam and Midazolam for the Sedation of Autistic Patients During Dental Treatment

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Abstract

Purpose: This study was undertaken to compare the effectiveness of oral diazepam and midazolam in sedating autistic patients during dental treatment.

Methods: The treatment regimen consisted of nitrous oxide/oxygen inhalation in conjunction with oral administration of either diazepam 0.3 mg/kg or midazolam 0.5 mg/kg in a cross-over design study of 13 subjects aged 5.8 to 14.7 years. A drug was classified as being effective when over 70% of the patients taking the drug were judged as “success” in all 3 behavioral criteria: (1) sleeping; (2) body movement; and (3) crying behaviors. The study was observed by an independent clinician with an intraexaminer reliability of 88%.

Results: For sleeping behavior, midazolam was found to be significantly more effective than diazepam as the duration of stimulation increased (P < .05). For the movement and crying behaviors, midazolam also proved to be significantly more effective from the start of treatment through the 35- and 40-min markers, respectively (P < .05). For the remainder of treatment, however, there was no statistically significant difference in these behaviors between the trials (P > .05). Diazepam and midazolam were rated as 77% and 100% successful, according to the overall behavior evaluation criteria (P = .02).

Conclusions: Both diazepam and midazolam were shown to be effective sedative agents, successfully and safely used to sedate autistic patients for dental treatment. Midazolam was significantly more effective than diazepam in those portions of the procedure with increased stimulation. (Pediatr Dent 2005;27:198-206)

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Autism was first described in 1943 by psychiatrist Leo Kanner.1 Autism is categorized as a pervasive developmental disorder2,3 and is characterized by abnormal emotional, social, behavior and linguistic development. To be diagnosed autistic, an individual must exhibit qualitative impairments in social interaction and communication, and show deviant patterns of behavior, interest, or activities. Some of these individuals are likely to exhibit mental retardation and self-injurious behavior.4-6

Autistic individuals exhibit increased susceptibility to dental caries and a high risk of periodontal disease due to a preference for soft and sweet foods, poor masticatory coordination, and food pouching.5

This is compounded by the difficulty in caring for the dental hygiene of these individuals. Nevertheless, other studies sometimes note the caries rate and prevalence of periodontal disease as not remarkably different from nonautistic individuals.7,8 Therefore, the main challenge to dentists may be the reduced ability of autistic patients to communicate to others.

Further problems include hyperactivity, limited attention span, low frustration threshold, hypersensitivity, and exaggerated reactions. Patients with autism dislike changes in their environment and need sameness and continuity; they may react with tantrums, screaming, or crying over small environmental changes.4-6 In dental treatment, if appropriate behavior management is ineffective and the use of aversive techniques is not appropriate, sedation may be
necessary to enable routine dentistry to be performed. As there are few medical problems associated with autism that are related to sedation, sedation of this patient group is permissible with no increased medical risk over that experienced in the normal population.

Several authors have recommended the use of sedation for autistic dental patients. Although nitrous oxide, chloral hydrate, hydroxyzine, and diazepam are frequently used in pediatric dentistry, they are administered by different routes and in different dosages and regimens and the success of these various techniques is unpredictable.

Nitrous oxide/oxygen inhalation alone or combined with chloral hydrate and/or hydroxyzine was reported as rendering unsatisfactory sedative effects in the dental treatment of autistic patients. Braff and Nealon reviewed the successful management of a small group of autistic dental patients with sedation. They concluded that various sedative agents may be effective and that a combination of drugs may be successful. In their study, the combination of diazepam and chloral hydrate or hydroxyzine exhibited a good sedative effect in autistic patients and supported the cases studied by Lowe and Jedrychowski, which indicated and recommended using a diazepam and hydroxyzine combination with nitrous oxide/oxygen as an acceptable sedation technique for autistic dental patients.

Fukuta et al. investigated the sedative effect of intranasal midazolam 0.2 mg/kg, supplemented with nitrous oxide/oxygen inhalation, in the provision of dental treatment for handicapped children, including autistic patients. They found that midazolam exhibited a successful sedative effect at the beginning of dental treatment. The technique they documented in this study was convenient and effective without any serious adverse effects. Van der Walt and M oran also found oral midazolam to be an effective premedication for mildly autistic patients who required general anesthesia for medical procedures.

Both diazepam and midazolam are sedative-hypnotic drugs in the benzodiazepine group. Diazepam is most commonly used as an anxiolytic with a broad margin of safety and exhibiting few side effects and is widely accepted as a sedative agent in pediatric dentistry. The recommended dosage of oral diazepam is 0.15 to 0.5 mg/kg, and a maximum single dose is 10 mg. It is effective in 30 to 45 minutes via oral administration and has a duration of action of 4 to 6 hours. In addition, some studies show that diazepam produces a sedative effect in uncooperative, handicapped children during dental treatment. Most clinicians favor the administration of a single dose of oral diazepam 45 to 60 minutes before treatment so that the medication is entirely under the control of the clinician and not open to misuse. Moreover, studies utilizing an approximate 0.3 mg/kg oral dose of diazepam have reported successful sedative effects during the subsequent dental treatment.

The common side effects of diazepam are drowsiness and ataxia. At the recommended doses for oral sedation, the most likely adverse effect is continued sedation in the postoperative period.

Much interest has been focused on the use of midazolam for conscious sedation in children. Midazolam, widely used as a preanesthetic sedative in both adults and children, has been shown to consistently provide successful behavior management and adequate safety. Oral midazolam is rapidly absorbed from the gastrointestinal tract, with peak plasma levels reached by 30 minutes, and has a duration of action of 45 to 60 minutes. The strong sedative effect of midazolam is remarkable, particularly because it has been shown to be very safe and exhibit few side effects.

Nevertheless, problems can arise if used in high-dose IV administration or when combined with other drugs—particularly opioids or central nervous system depressants. The few side effects associated with high doses of midazolam are nausea, vomiting, and respiratory depression. The recommended dosage of oral midazolam in the pediatric patient is 0.25 to 1 mg/kg, with a maximum single dose of 20 mg. Previous studies using 0.5 mg/kg oral midazolam have shown satisfactory sedative effects.

Diazepam and midazolam differ in many aspects, though they do share several significant traits. Both have the same mechanism of action and nearly the same clinical effects on the patient. Differences in their onset and duration of action result from a difference in biochemical properties. Few investigations compare diazepam to midazolam as a sedative agent with pediatric dental patients. Moreover, no studies on the sedative effects of both drugs in the autistic patient have ever been published.

The purpose of this study was to compare the effectiveness of 0.3 mg/kg oral diazepam with 0.5 mg/kg oral midazolam in sedating uncooperative, autistic patients for dental treatment.

Methods

Subjects

The sample consisted of autistic patients who received treatment at Yuwraprasart Walthayopramthum Child Psychiatric Hospital, an autistic treatment center. The inclusion criteria were:

1. medical diagnosis of autism;
2. age range from 5 to 15 years old;
3. categorization in American Society of Anesthesiologists II due to an autistic disorder;
4. at least 2 and not more than 4 sextants requiring restorative dentistry;
5. combative or uncooperative behaviors exhibited on the first examination visit;
6. a score of 0 to 7 on the assessment criteria that 2 of the authors have developed;
7. informed consent obtained from the patient's parents.

Thirteen subjects, consisting of 10 males and 3 females ranging from 5.8 to 14.7 years of age (mean=8.68), met the criteria. Each patient in this study required only 2 treatment visits.
Subjects were excluded from the study if they: (1) did not follow the preoperative instruction; (2) rejected administration of the sedative agent; or (3) failed to keep both sedation appointments.

**Study design**

This study was designed as a prospective, randomized, double-blind, cross-over trial and had the approval of The Ethics Committee of the Faculty of Medicine, Chulalongkorn University. Informed consent was obtained from the parents.

Patients were randomly allocated to receive diazepam or midazolam at their first appointment. The patients’ 2 appointments were separated by at least 1 week. The alternate drug was administered at the second appointment. A dentist, working under the supervision of an anesthesiologist, was responsible for both administering the sedative and providing dental treatment, and was assisted by 2 appropriately trained dental assistants. An independent observer (a registered nurse) monitored the patient’s clinical status and vital signs throughout each session.

All patients were instructed to fast for 6 hours prior to each session, according to the American Academy of Pediatric Dentistry’s guidelines. At the beginning of each appointment, health and oral fluid/food intake status was reviewed with the parent. Baseline vital signs of oxygen saturation, blood pressure, and heart rate were obtained using a pulse oximeter (Datasonde, Datasonde Corp, Paramus, NJ). Additionally, the nurse monitored respiratory rate.

After baseline measurements were obtained, either oral diazepam (Diazepam, GPO, Bangkok, Thailand) 0.3 mg/kg (maximum dose=10 mg) or midazolam (Dormicum-Roche, Basel, Switzerland) 0.5 mg/kg (maximum dose=20 mg) was given. These doses have shown themselves to be effective for sedation and also safe when used as premedication. Patient weight ranged from 15 to 63.2 kg (mean=43.4 kg). The mean dose of diazepam administered was 8.4 mg (range=5 to 10 mg), while the mean dose of midazolam was 15.8 mg (range=7.3 to 20 mg). Four patients had weights over 40 kg and received less than 0.3 mg/kg oral diazepam and 0.5 mg/kg midazolam, because they received each drug at the maximum dose.

Diazepam and midazolam were administered between 45 to 60 minutes and 20 to 30 minutes, respectively, prior to treatment to ensure an adequate sedation level. The patient was monitored in a quiet room under the supervision of the parent and the operator during the waiting time before being escorted to an operating room.

Patients were placed in a Papoose Board (Olympic Medical Corp, Seattle, Wash) and then monitored with a pulse oximeter every 15 minutes and with a precordial stethoscope continuously throughout the period of sedation, dental treatment, and recovery. The clinical signs monitored included the level of oxygen saturation, heart rate, blood pressure, respiratory rate, color, and heart and breathing sounds.

The nitrous oxide/oxygen mix was given via nasal mask at 50/50 for rapid induction in the first 5 minutes of treatment and at the injection period. A ratio of 40/60 was chosen for the rest of the treatment time. Upon completion of the treatment, the nitrous oxide was switched off and 100% oxygen was administered for 5 to 10 minutes before the nasal mask was removed.

Lidocaine 2% with epinephrine 1:100,000 was injected, and a rubber dam was applied in a standard technique for each treatment session. Dental treatment was given for a duration of 60 minutes. The procedures were: (1) restorations; (2) endodontic treatment; (3) stainless steel crowns; (3) scaling; (4) primary teeth extractions; and (5) sealant and fluoride applications. Once the dental treatment was completed, the patients were transferred to the recovery area and allowed to recover for at least 1 hour with their parents and the dentist. The criteria for discharge were: (1) vital signs within normal limits; and (2) responsiveness returning to preoperative levels.

Full written and verbal postoperative instructions were provided. Parents were contacted by phone 24 hours after treatment to assess patient postoperative health status and identify any complications.

**Behavior assessment**

Videotapes of the patients undergoing conscious sedation were recorded and used for behavior assessment by 1 independent rater. The Houpt sedation rating scale was modified for behavior evaluation of this study. A pilot study was conducted in a similar manner to the actual procedures to evaluate intraexaminer reliability. Videotape viewings of 4 sedative visits were conducted 1 month apart. There was an 88% agreement.

The behavior parameters were assessed by the rater at specific events: (1) Papoose Board placement; (2) injection; (3) rubber dam application; and afterward (4) every 5 minutes for the 60-minute treatment period. The rating of sleep, crying, and body movement for this study followed the Houpt scale (Table 1). The overall behavior score was derived from the mode of the sum of 3 behavior scores within 60 minutes (Table 2). It was used to categorize autistic patients into 4 groups: (1) “very good”; (2) “good”; (3) “fair”; and (4) “poor”—scored as a function of their behavior in relation to sedation and treatment. The data for overall evaluation were dichotomized according to success of the sedation. Evaluations of “good” and “very good” were classified as “success.” The authors defined the drugs as effective if over 70% of the patients to whom the drugs had been administered were rated as “success.”

**Data analysis**

This study was designed such that each patient served as his/her own control, with time of day, operator, and situation being relatively similar between the 2 treatment visits. Findings of sleep, crying, and body movement score were analyzed for statistically significant differences between
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Since the rating scales used the ordinal data with related samples, the nonparametric Wilcoxon matched paired signed rank test was used at the 95% level of significance. In addition, the chi-square test was used at the 95% level for comparison of the overall effectiveness of the drug regimens.

Results

Onset of sleep
Eight patients (62%) who received diazepam were calm and drowsy at the end of the pretreatment period (45 to 60 minutes), while 5 were not visibly affected. All of the patients (100%) who received midazolam were quiet and sedated between 20 to 30 minutes after the drug was administered.

Evaluation of sleep
The sleep effects of diazepam and midazolam were scored, respectively, for the 60 minutes as follows: (1) 75% and 67% drowsiness; (2) 14% and 6% awake; (3) 11% and 27% asleep. The sleep score decreased with time, and the Friedman test indicated a statistically significant difference between the 50- and 55-minute intervals ($P = .03$) for diazepam and between the 40- and 45-minute intervals ($P = .03$) for midazolam.

The mean rating score for sleeping behavior for each drug group appears in Figure 1. When the Wilcoxon test was used to compare diazepam with midazolam, the result demonstrated a statistically significant difference at the time of: (1) placing the patient in the Papoose Board; (2) administration of local anesthesia; (2) rubber dam application; and (3) the 20-minute interval ($0.02 < P < 0.04$). No significant difference was noted between diazepam and midazolam for the rest of the evaluation period ($0.16 < P < 0.65$).

Evaluation of crying
The frequency of crying with diazepam and midazolam was evaluated, respectively, over the 60 minutes as: (1) 43% and 68% not crying; (2) 23% and 20% mild crying; (3) 18% and 11% moderate continuous crying; and (4) 15% and 1% hysterical crying. The results indicated that there were minimal or moderate changes in diazepam-receiving patients between all 5-minute intervals. No statistically significant difference was observed, however, among the time intervals for 60 minutes ($P = .82$). In midazolam-administered patients, however, the results indicated that the crying score decreased with time and there was a statistically significant difference between the 50- and 55-minute intervals ($P = .02$).

The mean rating score for crying of each drug group appears in Figure 2. The Wilcoxon test showed statistically significant differences between the 2 drugs from the start of treatment through the 40-minute interval ($0.01 < P < 0.05$),
but no significant difference for the remainder of evaluation time (.16 < P < .76).

Evaluation of body movement
The effects of diazepam and midazolam on the frequency of each body movement score were evaluated, respectively, as: (1) 28% and 58% no movement; (2) 40% and 34% mild movement; (3) 30% and 7% moderate continuous movement; and (4) 3% and 1% violent movement through the rating time. The results of the diazepam-administered group indicated that there was no statistically significant difference among the time intervals for 60 minutes (P = .78). In contrast, the body movement of the midazolam-sedated patients increased with time, and there was a significant difference between the 45- and 50-minute intervals (P = .04).

The mean rating score for body movement of each drug group appears in Figure 3. The Wilcoxon test indicated statistically significant differences between the 2 drugs from the start of treatment until the 35-minute interval (P < .04), but no significant difference for the rest of the evaluation period (P > .00).

Overall evaluation
At the conclusion of treatment, each administration was evaluated for overall effectiveness. Analysis using the Wilcoxon test indicated statistically significant differences from the start of treatment until the 30-minute interval and at the 40-minute interval (.01 < P < .04), but no significant difference for the rest of the evaluation period (.08 < P < .96), shown in Figure 4.

The data for overall evaluation categorized the patients into 4 groups: (1) “very good”; (2) “good”; (3) “fair”; and (4) “poor” (Table 3). The overall behavior groups were dichotomized to represent the success or failure of the sedative drug. Ten of the 13 patients (77%) who received diazepam and all (100%) of the patients who received midazolam were rated in the “good” and “very good” categories and, therefore, classified as “success.” These results demonstrated the success of both diazepam and midazolam as sedative drugs, but there was a statistically significant difference in overall effectiveness when compared using the chi-square test (P = .02).

Discussion
This study demonstrated that both midazolam and diazepam provided conscious sedation of autistic patients with some significant differences. For sleeping behavior, both drugs rendered patients calm and drowsy for almost all the rating period (60 minutes). Nevertheless, the effect promoted by both drugs decreased over time, particularly in the
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Midazolam showed higher effectiveness in regulating sleep, body movement, and crying behavior, and it induced a homogenous response in the patient. This drug did, however, provide a shorter duration of action. Diazepam, while providing a longer duration of action, was less effective and produced a higher variation response in the resulting patient. This is consistent with findings of past studies on the properties of both drugs in uncooperative, nonautistic children. Midazolam had higher effectiveness than diazepam in normal children, as in the autistic patients of this study. Diazepam had a longer duration of action in normal and autistic children (45 to 120 minutes).

Midazolam, however, can improve child patient cooperation for approximately 45 to 60 minutes. The more rapid onset and more predictable responses of midazolam found in this study are similar to previous reports of its effect in normal children.

A few previous investigations studied sedative effects in autistic patients. These studies were either retrospective or not specific to autistic individuals, however, and they employed intravenous or intranasal as administration routes that are particularly difficult for autistic children.

This is the first known study to examine and compare the use of oral diazepam with midazolam, combined with nitrous oxide/oxygen inhalation for the conscious sedation of autistic

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**Figure 3.** Mean rating score of body movement in each drug group. *Statistically significant difference between drug groups (P < .05).

**Figure 4.** Mean rating score of overall scores in each drug group. *Statistically significant difference between drug groups (P < .05).
dental patients. This study used appropriate controls in a representative sample of subjects set to reliable criteria, double-blind concealment, and random allocation of subjects to experimental conditions.

There were some limitations and confounding factors in this study. The fixed onset time (diazepam=45 to 60 minutes, midazolam=20 to 30 minutes) may not be appropriate for a patient who responds to the drugs differently than others, particularly diazepam—due to the higher variation of patient response to this medication. This study used only 1 dose of each medication; other doses in the recommended range (0.15 to 0.5 mg/kg oral diazepam and 0.25 to 1 mg/kg midazolam) may yield different results. In this study, 4 patients were administered a lower drug dose by weight than other participants because they received the drugs at the maximum allowable dose in the study protocol. Therefore, the behavior of these 4 patients might have been divergent from other patients.

Nevertheless, investigation of the data revealed no remarkable difference in the 3 specific behaviors resulting from these dosages, as compared to the remainder of the group. A statistical conclusion could not be made, however, due to the small sample set. The limited rating time of this study restricted the comparison of both drugs beyond 60 minutes. Therefore, behaviors beyond this duration were not observed. In addition, the sedative effect in this study was not obtained purely from oral diazepam or midazolam, because nitrous oxide was also utilized—rendering an analgesic, synergistic action with the oral drugs. Nitrous oxide may have attenuated behavioral responses of this study’s patients.

This study did not observe any identifiable second-appointment effects, as the observations of first visit behavior against second visit behavior were found to be statistically insignificant (P=0.67, for diazepam, P=0.43 for midazolam). To better test for these effects, a study might dictate comparing an alternating drug regimen over 4 treatment visits against a control set, wherein diazepam is administered to half the patients each time and midazolam is administered to the other half each time. All patients in this study needed only 2 appointments to complete the treatment. Given the nature of this study, it is not appropriate to draw any conclusions on this subject.

No undesirable effects for patients receiving either diazepam or midazolam were observed in this study. Crucial safety concerns for the clinician considering conscious sedation with diazepam or midazolam are:

1. appropriateness of the selected patient made in consultation with the physician for undergoing sedation;
2. availability of sufficient essential equipment;
3. availability of backup staff in case of emergency during treatment.

As oral sedation cannot be titrated to the individual’s response, anyone undertaking this technique must be competent in managing problems or emergencies.

**Conclusions**

Based on this study’s results, the following conclusions can be made:

1. Oral diazepam 0.3 mg/kg and midazolam 0.5 mg/kg both appear to be safe and effective sedative agents for autistic patients 5 to 15 years of age.
2. Both drugs are effective sedative agents; however, midazolam is more effective in regulating patient behavior at times of increased stimulation.
3. The sedative effect of midazolam is shorter (30 to 45 minutes), while diazepam yields a longer duration of action (60 minutes).

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**References**


Consumption of nonpublic water, either bottled or from rain barrels, may put children at increased risk of caries because the water is nonfluoridated. The aim of this study was to investigate the relationship between consumption of nonpublic water, socioeconomic status (SES), and caries experience in the primary and permanent dentition. A random sample of 9,988 children in the Australian School Dental Service participated. Forty-five percent of children had greater than a 50% lifetime consumption of nonpublic water, while 36% had 0% lifetime consumption. Increased use of nonpublic water was found for children from lower SES groups, 2-parent families, and rural areas. These results were likely a result of the children's residential location. Multivariate modeling revealed a significant positive relationship between caries in the primary dentition and consumption of nonpublic water—even after controlling for the child's age, sex, SES, and residential location. This relationship was significant only for those children with 100% access to fluoridated water. The effect was not significant in the permanent dentition. Dental professionals should continue to lobby for the addition of fluoride to bottled water, given that younger children drinking nonpublic water are more at risk to caries in the primary dentition and consumption of bottled water is reportedly increasing.

Comments: These cross-sectional results are from a large data set collected in Australia between 1991 and 1995. Despite the data set's age, few studies have been conducted on the relationship between drinking nonpublic water and caries experience. For children who have 100% access to fluoridated water, those who drink water from a nonpublic source are at greater risk of caries in the primary dentition—even after controlling for socioeconomic characteristics. It was interesting that this result was not found in the permanent dentition. One possible reason for this difference is that older children may be substituting bottled water for carbonated beverages that are generally consumed in large amounts during adolescence. Additionally, the permanent dentition's high prevalence of sealants and diminished susceptibility to caries compared to primary teeth may also explain this difference. This study did not differentiate between children drinking water collected in rain barrels and those drinking bottled water. The drinking of water collected in rain barrels (tanks) may be more common in Australia than in most of North America. It is promising to note that at least 20 US companies produce bottled water with optimum fluoride concentrations. These brands should be recommended to our patients. Unfortunately, many parents turn to bottled water to avoid what they consider “chemicals,” like fluoride, added to their community water supplies. Thus, they may intentionally avoid bottled water that has been optimally fluoridated.

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