The Effects of Midazolam on Pediatric Patients with Asthma

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Abstract

Purpose: This study was performed to evaluate the safety and efficacy of midazolam in asthmatic patients undergoing dental treatment.

Methods: Twenty-four children, aged 19 to 65 months, with a diagnosis of mild to moderate asthma were given an oral dose of 0.5 mg/kg of midazolam. Oxygen saturation, respiratory rate, and pulse rate were monitored before, during, immediately after, and 30 minutes following dental treatment. The child's asthma score was also determined before and after treatment. The dental operator assessed the overall sedation outcome immediately after treatment.

Results: Twenty-three of the 24 subjects had asthma scores of "0" before and after treatment. During dental treatment, 2 patients had oxygen saturations of 94% at one point during treatment. However, oxygen saturation increased when the patient's head and neck were repositioned. Twenty-three of the 24 subjects had oxygen saturations above 95% at 30 minutes following treatment. Pulse rates and respiratory rates exhibited transitory increases, linked to when the child was stimulated. Statistical analysis was conducted from within subjects repeated measures via ANOVA and with a general linear model approach. No statistically significant differences occurred in oxygen saturation and respiratory rate. However, significant differences did occur in pulse rate between 5 and 10 minutes (mean difference=10±3.84) and between 10 and 15 minutes (mean difference=19±5.50), as expected. No statistically significant differences occurred in asthma score before and after treatment. Twelve subjects were assessed to have excellent behavior, 5 subjects were satisfactory, and 7 subjects were unsatisfactory. No treatment was aborted.

Conclusions: With adherence to the AAPD's sedation guidelines, midazolam at a dose of 0.5 mg/kg is a safe and effective mean for sedation of patients with mild to moderate asthma. (*Pediatr Dent*. 2003;25:137-142)

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Asthma is an inflammatory disorder of the airways causing the release of multiple inflammatory mediators such as histamine, leukotrienes, and prostaglandins.[1] These result in bronchoconstriction, excessive mucus secretion, exudation of plasma, and airway hyperresponsiveness. The symptoms are usually associated with widespread but variable airflow obstruction that is often reversible, either spontaneously or with treatment.[1] Asthma is the most common chronic respiratory illness of childhood. Although people of all ages are affected by asthma, most cases of asthma begin in childhood, and peak prevalence occurs between the ages of 6 and 11 years.[2] It is estimated that 5% to 15% of children (approximately 1 in 10 children) have asthma, including more than 4 million children less than 15 years of age.[3] In the United States, the number of asthma cases has risen by 60% since the early 1980s.[4] Over 5,000 Americans die each year from asthma.[4] The prevalence of asthma is higher in industrial countries and is greater in urban than in rural populations.

The prevalence is increasing worldwide, and hospital admissions, especially among children, are on the increase. It is the leading cause of pediatric hospitalization and accounts for

nearly 1% of all US medical expense.[5] In 1997, the National Institutes of Health Expert Panel Report 2 classified asthma severity into mild-intermittent, mild-persistent, moderate-persistent, and severe-persistent.[6] The signs and symptoms of each classification of asthma are summarized in Table 1. According to the updated National Asthma Education and Prevention Program guidelines, the treatment of mild-intermittent asthma requires a short-acting bronchodilator (BD) such as inhaled ß$_2$-agonists on an as-needed basis.[6] Mild-persistent asthma is treated with an inhaled corticosteroid (ICS) or other anti-inflammatory medication.[6] Treatment of moderate-persistent asthma requires a moderate to high dose ICS and a long-acting BD, while severe-persistent asthma is treated with a high dose ICS, a long-acting BD, and oral steroids.[6] Use of a short-acting inhaled ß$_2$-agonist is required with any acute exacerbation, regardless of the severity of the underlying asthma condition.[6]

In pediatric dentistry, a wide array of techniques is used to manage patient behavior. Today, common practice includes the use of medications for conscious sedation. A variety of drug regimens are used when young children are sedated for dental treatment. Many studies have been done on the effects of these sedatives. However, few studies have been done evaluating the relationship between the effects of sedation and common childhood diseases. A 1993 study by Haney et al, evaluated the success of meperidine and promethazine sedation in medically compromised patients.[7] Participants of that study included those with cerebral palsy, mental retardation, cardiac disease, chronic liver disease, childhood cancers, and spina bifida, however, there were no conditions that affected respiration. In addition, that study did not include a statistical analysis of vital signs. Therefore, the effects of meperidine and promethazine on respiration could not be evaluated.[7]

Conscious sedation may be achieved with a number of agents, including narcotics, barbiturates, benzodiazepines, and other drugs. Narcotics, while an effective means of sedation, may be a poor choice for asthmatic patients because they may cause histamine release.[8] This histamine-releasing potential could precipitate a severe asthma attack in the dental office which may not be equipped to handle such a situation. Meperidine and congeners have histamine-releasing potential, although less than morphine.[9] Sufentanil and fentanyl have less histamine-releasing potential, but these are not available for oral administration.[9] Fentanyl is available as a solid matrix lozenge for transmucosal absorption. However, this requires a schedule II prescription and may result in unacceptable levels of sedation and respiratory depression due to difficulty with dosing.[9] Both narcotics and barbiturates have been contraindicated in asthmatic patients because they can potentially depress the respiratory drive. An older study by Aldrete et al determined the effects of chloral hydrate on the respiration of nonasthmatic and asthmatic patients.[10] This study found that 20 mg/kg of chloral hydrate did not produce a marked depression of respiration in either healthy adult subjects or asthmatic patients.[10] However, the oxygen saturations remained lower in asthmatic patients at a 3 hours following evaluation.[10]

Table 1. Classification of Asthma

Mild-intermittent	Symptoms less than or equal to 2 times a week
	Exacerbations brief (few hours to few days); intensity may vary
	Nighttime symptoms less than or equal to 2 times a month
Mild-persistent	Symptoms greater than 2 times a week but less than 1 time a day
	Exacerbations may affect activity
	Nighttime symptoms greater than 2 times a month
Moderate-persistent	Daily symptoms
	Daily use of inhaled short-acting ß$_2$-agonist
	Exacerbations affect activity
	Exacerbations greater than or equal to 2 times a week, may last days
	Nighttime symptoms greater than 1 time a week
Severe-persistent	Continual symptoms
	Limited physical activity
	Frequent exacerbations
	Nighttime symptoms are frequent

Benzodiazepines are very useful because of their anxiolytic and sedative properties; however, they provide no analgesia.[11] Benzodiazepines work by binding to a receptor complex which facilitates the action of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).[11] The use of midazolam for conscious sedation in children has become a common practice in pediatric dentistry. Midazolam is a short-acting benzodiazepine that has hypnotic, anticonvulsant, muscle-relaxant and anterograde amnesic effects.[12] While midazolam has proven to be effective and has a wide margin of safety, there are some risks that should be considered. The most serious adverse events associated with the use of midazolam in the pediatric population include hypoventilation, decreased oxygen saturation, a dose-related risk of apnea, laryngospasm, and hypotension.[11] The following events related to the use of IV midazolam in children have been reported: desaturation in 5% of subjects, apnea in 3%, and hypotension in 3%.[13] In a study using midazolam as a sedative agent in fiberoptic bronchoscopy, it was noted that 35% of midazolam-sedated patients had oxygen desaturation episodes despite routine supplemental oxygen.[14] Contributing factors to desaturation included respiratory depression and upper airway obstruction due to excess sedation and supine position, among other causes.

Another concern is that in about 6% of the population, midazolam has a delayed metabolism leading to accumulation

of the drug with consequent prolongation of its action.[14] However, Humbert et al reported that fiberoptic bronchoscopy is well tolerated in asthmatic patients.[15] In their study, subjects were given salbutamol by nebulizer 10 to 15 minutes before the examination and IV midazolam immediately before the procedure.[15] Despite these concerns, several studies have compared different sedative regimens and have determined midazolam to be an effective sedative for conscious sedation in healthy children.[16-18] Interestingly, a study conducted in 1994 by Silver et al evaluated 2 dosages of oral midazolam as a conscious sedation medication for physically and neurologically compromised pediatric dental patients.[19] This study found that there were no clinical signs of a compromised respiratory rate with use of a 0.3 mg/kg or 0.5 mg/kg dosage. As of yet, there has been no study in the dental literature to determine midazolam's effect on asthmatic patients.

Because of the limited information available, there has been some concern expressed about the use of midazolam on pediatric patients with asthma. However, asthmatic patients cannot be excluded with regards to methods of behavior management. There should be a greater interest in safely managing these patients without the fear of inducing an asthma attack after sedation in the dental chair. The issue of respiratory depression should be of common concern to all pediatric patients and should not be considered unique for asthmatics. This study was performed to evaluate the effects of a standard oral dose of midazolam in asthmatic patients undergoing dental treatment.

Methods

Patient selection

This study was approved by the Wayne State University and the Detroit Medical Center Human Subject Committee. The procedures, possible discomfort, and/or risks as well as possible benefits were explained fully to the parents of the subjects included in this investigation, and informed consent was obtained prior to enrolling the patient in this study. Twenty-four children, 17 males and 7 females, were enrolled in this study. The ages of the children ranged from 19 to 65 months with a mean age of 36.6 months and a mean weight of 35.4 lbs (ranging from 21 lbs to 72 lbs). Each child had a diagnosis of mild to moderate asthma based on a consultation with the parents and/or the child's physician. The severity of asthma was determined based on the classification previously mentioned. Of the 24 patients, 21 had a diagnosis of mild-intermittent or mild-persistent asthma, while the remaining 3 had a diagnosis of moderate-persistent asthma.

Exclusion criteria included the following:

1. presence of a medical contraindication for sedation;
2. children with allergy to midazolam;
3. children with severe-persistent asthma or an asthma score of 2 at initial examination.

Table 2. Asthma Score Classification*

Indicator	0	1	2
SpO_2	>94% (air)	<94% (air)	<94% (40% O_2)
Cyanosis	No	Yes	Yes
Breath sounds	Equal	Unequal	Absent
Wheezing	None	Moderate	Marked
Accessory muscles	None	Moderate	Marked
Level of consciousness	Alert	Agitated or depressed	Comatose

*Modified from Wood et al, 1972.

Inclusion criteria consisted of the following:

1. children ages 12 to 72 months;
2. children with a diagnosis of mild-intermittent, mild-persistent, or moderate-persistent asthma at initial examination;
3. children in need of sedation for behavior management due to age or level of cooperation;
4. children in need of routine restorative work and/or extractions.

Preoperative assessment and medication administration

On the day of dental treatment, subjects presented without food or fluids ingestion for at least 4 hours prior to treatment. Before the medication was administered, the evaluation of breathing was done with the aid of a nurse from the department of pulmonary medicine at Children's Hospital of Michigan. A preoperative assessment was made and a modified asthma score was used to assess the patient's respiratory status (Table 2).[20] In addition to the asthma score, the baseline respiratory and pulse rates were determined. A numerical value was given to indicate asthma score based on the highest indicator value. Oxygen saturation and pulse rate were monitored with the Nelcor pulse oximeter, and respiratory rate was measured by observation by the nurse. Each child was then given 0.5 mg/kg of midazolam orally. The sedative was administered to the child by the dentist with the aid of the parent. After 10 minutes, the child was separated from the parent(s) and taken into the treatment room where the pulse oximeter monitor was affixed. The children were not initially wrapped in a papoose board. Disruptive behaviors that were considered potentially harmful to the child or dental team resulted in the use of the papoose board, with parental consent, for the remainder of treatment. For treatment in which local anesthesia was necessary, 2% lidocaine with 1:100,000 epinephrine was used. For all subjects, no more than 2 Carpules of anesthetic were used. A rubber dam was placed where necessary. Additionally, for all treatment, supplemental nitrous oxide/oxygen or oxygen alone was not used.

Evaluation of respiratory function and vital signs

During treatment, oxygen saturation and pulse and respiratory rates were determined every 5 minutes. Treatment

Table 3. Behavior Assessment*		
0	Excellent	Patient treated without difficulty; minimal crying; patient quiet/ asleep for most of treatment
1	Satisfactory	Patient treated with minimal difficulty; some struggling/crying but not continuous throughout procedure
2	Unsatisfactory	Patient treated with difficulty; struggling/crying continuous throughout procedure
3	Aborted	Patient treatment not completed; increased risk to patient and dental team

*Modified from Leelataweewud et al, 2000

time ranged from 15 minutes to 45 minutes. At the end of dental treatment, asthma score and pulse and respiratory rates were again determined using the criteria mentioned above. Oxygen saturation and pulse and respiratory rates were then recorded at 30 minutes following treatment.

Behavior assessment

Immediately after treatment, the dental operator assessed the overall sedation outcome using a subjective scale described in Table 3.[21]

Results

Evaluation of respiratory function

Twenty-three of the 24 subjects presented with initial asthma scores of "0." The 1 subject with an asthma score of "1" had a diagnosis of moderate-persistent asthma with daily use of albuterol. Wheezing was present before and after treatment; however, oxygen saturation consistently remained above 95%. It was also noted by the nurse that there was less or minimal wheezing immediately after treatment.

During dental treatment, there were fluctuations in oxygen saturations. For all subjects except 2, oxygen saturations remained normal and consistently above 95% throughout the entire procedure. There were 2 subjects whose oxygen saturations fell down to 94% at some point during treatment. However, oxygen saturation increased when the patient's head and neck were repositioned. Both of these subjects had posttreatment asthma scores of "0" and oxygen saturations of 98% and 97% 30 minutes following treatment, respectively.

After treatment, 23 out of 24 subjects again had an asthma score of "0" (with the same patient with an initial asthma score of "1" receiving a posttreatment score of "1"). Of the 24 subjects, 23 had oxygen saturations above 95% at 30 minutes following treatment. One subject left the dental clinic without notification to the operator before the 30-minute postoperative evaluation could be made.

Evaluation of vital signs

There were few changes in vital signs throughout the procedures. Pulse rates and respiratory rates exhibited transitory increases. In these cases, changes were linked to specific occurrences when the child was stimulated (for example, local anesthetic injection). The increase in pulse rate was transitory and quickly returned to normal when the stimulus ended. With regard to respiratory rate, similar transitory changes occurred at a time of a particular stimulus.

Evaluation of behavior

Twelve subjects were assessed as "0," representing excellent behavior, 5 subjects were assessed as "1," indicating satisfactory behavior, and 7 subjects were assessed as "2," indicating unsatisfactory behavior. No treatment was aborted, therefore, no subject received a classification of "3" (refer to Table 3). Of the 24 subjects, 5 patients required the use of a papoose board due to lack of cooperation.

Treatment performed

Of all patients treated, 13 received Class I amalgam restorations, 7 received extractions, and the remaining 4 patients received stainless steel crowns.

Statistical analyses

All statistical procedures were conducted using the Statistical Package for Social Sciences (SPSS), Version 11.0. To examine mean differences across time points (5 minutes, 10 minutes, and 15 minutes) in oxygen saturation rates, respiratory rates, and pulse rates, a repeated measures analysis-of-variance (ANOVA) was employed. Although data was collected through 45 minutes, relatively few patients had complete data after the 15 minutes necessary for a balanced comparison of mean values. Pair-wise differences in means across the time points were considered statistically significant at $P \leq .05$, two-tailed. All appropriate assumptions were checked and verified.

Oxygen saturation rates

Oxygen saturation rates stayed relatively constant across the 3 time points (Table 4). No statistically significant differences in mean values occurred between 5 and 10 minutes or 10 and 15 minutes. Mean oxygen saturation dropped significantly between 5 minutes (99±1) and 15 minutes (98±2), with the mean difference of 1.25 (SE=0.36) considered statistically significant at $P \leq .01$. However, the drop in oxygen saturation was less than 4%; therefore, it was not clinically significant.

Respiratory rate

Similar to oxygen saturation rates, respiratory rates also stayed relatively constant across the 3 time points (Table 5). No statistically significant differences in mean values occurred between 5 and 10 minutes, 10 and 15 minutes, or 5 minutes and 15 minutes, and no clinically significant findings were observed.

Table 4. Oxygen Saturation

Oxygen saturation rate	Mean±SD	N
5 min	100±1	24
10 min	100±1	24
15 min	98±2	24

Table 5. Respiratoy Rates

Respiratoy rates	Mean±SD	N
5 min	28±9	24
10 min	28±6	24
15 min	30±6	24

Table 6. Pulse Rate

Pulse rate	Mean±SD	N
5 min	110±19	24
10 min	120±26	24
15 min	129±33	24

Pulse rate

Mean pulse rate values rose consistently from 5 minutes through 15 minutes (Table 6). Pulse rate values rose significantly from a mean of 110±19 at 5 minutes to a mean of 120±26 at 10 minutes (mean difference of 10: SE=4, *P*=.048). Similarly, pulse rate rose from a mean of 120±26 at 10 minutes to a mean of 129±33 at 15 minutes (mean difference of 9: SE=5, *P*=.169). The largest mean difference (19: SE=6, *P*=.006) was seen from 5 minutes to 15 minutes. Although there were statistically significant differences in pulse rates over the time period, these results were not clinically significant considering local anesthetic injection and initiation of treatment would increase pulse rate.

Discussion

The results of this study indicate that midazolam had little, if any, effect on selected asthmatic patients. Comparatively, a study conducted in 1999 by Fraone et al, assessed 61 healthy (ASA I) children aged 24 to 58 months presenting for restorative dental care. The participants in that study were of an age similar to those in this study's group, and the same dosage of midazolam was used. This study found no significant oxygen desaturations or clinically evident respiratory depression among subjects.[16] This study found similar results, with no adverse effects of this drug on pediatric asthmatic patients.

One subject, who had moderate-persistent asthma, had an initial and posttreatment asthma score of "1." During dental treatment, the subject's oxygen saturation was consistently above 95%. The wheezing that the patient had before treatment decreased after the dental treatment was completed. With these results, it can be concluded that, for this patient, midazolam produced no adverse effects on a patient with moderate-persistent asthma who presented with wheezing before treatment.

Although the effectiveness of sedation in behavior management was not a major outcome variable, this study did find that 50% of patients were rated with "excellent" behavior based on the behavior assessment scale. Twenty-one percent of patients had behavior rated as "satisfactory" (treatment completed with minimal difficulty), while 29% of patients were rated as "unsatisfactory" (patient treatment with difficulty). Considering that treatment time ranged from 15 to 45 minutes, the authors were pleased to find that success rates were high even in lengthier appointments. By combining excellent behavior and satisfactory behavior, this study found that 71% of patients were treated with minimal difficulty. These results are comparative to a study conducted by Wilson et al, who found that 67% of study participants earned a "good" behavior rating when sedated with midazolam.[18]

The results of this study should be of interest to all dentists who treat asthmatic patients. Uncooperative children present a challenge to dental treatment. However, a variety of options are available to treat healthy children. Asthmatic patients offer a different challenge that may make a dentist hesitant to treatment. According to Zhu et al, concerns arise when uncooperative asthmatic patients present for dental treatment. With increased stress levels and hyperactivity, asthmatic patients may become more susceptible to an asthma attack.[22] Sedation with midazolam may decrease anxiety and stress levels, resulting in a decreased probability of an asthma attack.

A limitation to this study is midazolam's short working time. Participants of this study presented with the need for routine dental treatment in single quadrants. For extensive dental work, it may be necessary for multiple visits or a different drug with longer effects.

Necessary precautions should be taken to assure patient safety throughout dental treatment. Resuscitative equipment should always be available because of the potential respiratory depressant effects of the drug. These respiratory effects may occur unexpectedly, especially in patients who are debilitated or who have a preexisting pulmonary disease, such as asthma. Flumazenil, the reversal drug for benzodiazepines, should be available when midazolam is administered. Although not included in the study protocol, the parents of the study subjects were urged to bring medications, nebulizers, and compressors with them to the dental appointment. However, none of the patients required any rescue medication after the procedure. It is recommended that careful and repeated monitoring be done on all sedation patients to affirm their safety (as outlined in the AAPD's sedation guidelines).[23]

Conclusions

1. Sedation with midazolam, when given orally at a dose of 0.5 mg/kg, produces little to no adverse effects on asthmatic patients presenting with mild to moderate symptoms.
2. Most patients were treated with minimal difficulty at a dosage of 0.5 mg/kg of midazolam.
3. With strict adherence to the AAPD sedation guidelines, midazolam is a safe and effective means of sedation for patients with mild to moderate asthma.

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