



Allergic Reaction to Intranasal Midazolam HCl: A Case Report

Michael McIlwain, DMD Robert Primosch, DDS, MS, MEd Enrique Bimstein, CD

Dr. McIlwain is a resident; Dr. Primosch is professor and associate dean for education; Dr. Bimstein is professor, Department of Pediatric Dentistry, University of Florida College of Dentistry, Gainesville, Fla.

Correspond with Dr. Bimstein at ebimstein@dental.ufl.edu

Abstract

An acute allergic reaction in a 5-year-old healthy male, after receiving midazolam by intranasal atomizer for sedation purposes in the dental clinic, was reported. Shortly after the midazolam was provided, the child developed urticaria in both ankles, which rapidly progressed to the lower extremities, stomach, back, arms, neck, and face. The periorbital skin also became edematous. In the emergency room, the diagnosis of an urticaria allergic reaction was confirmed. The child was treated with intramuscular diphenylhydramine, discharged from the emergency room after 5 hours, and prescribed oral diphenylhydramine (Benadryl) and prednisolone (Orapred). Children who receive sedatives such as midazolam in the dental clinic should be carefully monitored from the moment they receive the sedative, in order to disclose and treat undesirable side effects of the sedative agents as early as possible. The implications of allergic reactions to sedative agents in the dental clinic are reviewed. (*Pediatr Dent.* 2004;26:359-361)

KEYWORDS: MIDAZOLAM, ALLERGY, INTRANASAL SEDATION

Received June 4, 2003 Revision Accepted February 19, 2004

Conscious sedation is a valuable pediatric dentistry aid for children whose behavior cannot be managed with traditional management techniques. The desired level of sedation in a clinical setting has been described by the American Academy of Pediatric Dentistry (AAPD) as a controlled, pharmacologically induced, minimally depressed level of consciousness retaining the patient's ability to maintain a patent airway independently and continuously and to respond to physical stimulation and/or verbal command.¹

Moreover, the AAPD indicated the drugs, dosages, and techniques used for pediatric dental sedation must promote patient welfare and safety.¹

Therefore, pediatric dentists must limit themselves to the use of pharmacological agents promoting sedation with a wide safety range and minimal risk for dangerous side effects such as respiratory or cardiac arrest.

Despite the fact that commonly used sedative agents in pediatric dentistry are considered to have a wide safety range, aversive reactions such as nausea, vomiting, excessive sleep, and allergic reactions may still be encountered.²⁻¹¹ Midazolam hydrochloride is a water-soluble benzodiazepine that has a short-acting central nervous system (CNS) depressant effect.^{6,12} The manufacturer warns about midazolam's risks:

1. potential for respiratory depression and respiratory arrest when the drug is administered intravenously;

2. use with other CNS depression medications;
3. use in patients with acute narrow-angle glaucoma;
4. known hypersensitivity to the drug.¹⁰

Nevertheless, the use of midazolam in pediatric dentistry, either by oral or intranasal routes, is reported to be a safe and effective procedure.¹²⁻²⁹

Despite the manufacturer's warning against the use of midazolam in patients with a known sensitivity to the drug,¹⁰ the number of reports of hypersensitivity to this medication is minimal: the authors' review of the literature revealed only 2 cases.^{4,5} Because the welfare of the children is of paramount concern in pediatric dentistry, the dental clinician should be aware of the potential midazolam has for provoking an allergic reaction, and be ready to recognize and adequately treat it.

This article reports the case of a 5-year-old, who developed an immediate, acute allergic reaction to intranasal midazolam in the dental clinic.

Case report

A 5-year-old, 23-kg male, was scheduled for restorative treatment under conscious sedation using midazolam in the pediatric dental clinic at the University of Florida College of Dentistry. The child's systemic history indicated frequent ear infections, respiratory syncytial virus at age 6

weeks and 1 year, and asthma managed with albuterol inhaler as needed.

Conscious sedation was justified by behavior management difficulties during the treatment planning visit and extent of the dental treatment. Preoperative physical assessment confirmed a healthy patient, free of systemic illness in the last 10 days, normal vital signs for age, and a patent airway. Risk assessment placed him in the category of ASA I, and his NPO status was verified.

Since the parent indicated the patient would not drink any type of medicament, it was decided to utilize the intranasal route combined with nitrous oxide–oxygen inhalation sedation. The patient was administered 1 mL (5 mg) of midazolam (Midazolam HCl injection, American Pharmaceutical Partners, Inc, Schaumburg, Ill) by intranasal atomizer (MAD 300, Wolfe Tory Medical, Denver, Colo). After 3 to 4 minutes, the father reported that the child's ankles started to itch. Immediate examination of the child revealed urticaria at both ankles, which, within a few minutes, progressed to the lower extremities, stomach, back, arms, neck, and face. The periorbital skin also became edematous.

The patient was fully alert and not monitored with a pulse oximeter. There was no apparent respiratory distress, and it was decided to manage the reaction with the oral antihistamine agent diphenhydramine (Benadryl). As predicted by the parent, the child refused to cooperate with oral administration. Rather than give 25 mg diphenhydramine (50 mg/mL) intramuscularly, it was decided to transport the child to the emergency room, which was located a few minutes away from the dental clinic.

In the emergency room, about 20 minutes after midazolam administration, the patient reached a "floppy doll" (eg, a slow-to-react and relaxed state of sedation) stage. His vital signs were normal and diagnosis of an urticaria allergic reaction was confirmed. After 2 failed attempts to provide oral diphenhydramine (Benadryl 25 mg) and prednisolone (Prelone 21 mg) syrup because the patient spit the drugs out, 25 mg diphenhydramine was injected intramuscularly.

The urticaria receded gradually, and after 5 hours, the child was discharged from the emergency room with prescriptions to take oral Benadryl 25 mg every 6 hours for 3 days and prednisolone (Orapred) 7.5 cc twice a day for 3 days. Written instructions were also given to seek immediate medical attention in the case of recurrent urticaria or swelling. Follow-up telephone calls revealed no further complications of this adverse event, but it was uncertain if the parents had success administering the prescribed drugs by mouth at home. It should be noted the patient received subsequent dental treatment under conscious sedation with chloral hydrate and hydroxyzine orally by syringe, with no adverse reactions and achieved a successful sedation level.

Discussion

The basic function of the immune system is the protection of the body from infection and foreign substances or objects.³⁰ An allergic reaction involving hypersensitivity responses by the immune system may occur when an individual who has produced an IgE antibody response to an innocuous antigen or

allergen encounters the same allergen more than once. The allergen triggers the activation of IgE-binding mast cells in the exposed tissue, leading to a series of responses characteristic of allergies, including skin and respiratory reactions and inflammation. The intensity of the immune system reaction may be mild to severe, depending on the amount of histamine release. Severe reactions, such as anaphylaxis, are dangerous and may lead to death. In general, the more rapid the onset and intense the symptoms, the more severe the generalized reaction that can be expected.³⁰

Medications, which are used in principle to benefit the patient, have the potential to elicit an anaphylactic reaction. In pediatric dentistry, the primary agents that might provoke an allergic reaction are local anesthetics and latex.^{31,32} Sedative agents are rarely considered potential allergens, especially when given orally. However, a review of the literature includes allergic reactions to meperidine,^{2,3,11} chloral hydrate,⁹ and midazolam.^{4,5} Meperidine is particularly dangerous, since it has the potential to cause urticaria, abscesses, and anaphylaxis.^{2,3,11}

In this case report, midazolam was administered intranasally, which is regarded as a parenteral route of administration. The use of intranasal midazolam is very popular among clinicians when challenged by a recalcitrant, uncooperative child refusing to take medications orally.^{8,12} The intranasal route is particularly effective because of the rapid and high plasma levels achieved.²⁷⁻²⁹ An atomizer was selected for delivery because reports suggested nasal mucosa absorption was better and less painful than when drops were used.^{18,19,22}

Midazolam is considered a safe sedative agent in children. Rare adverse reactions reported have included respiratory arrest, respiratory depression, headache, oxygen desaturations, apnea, hypotension, paradoxical reaction, and hypersensitivity; however, very few cases of allergies have ever been reported. The child reported in the present manuscript, to the knowledge of his parents, had no prior exposure to midazolam. Therefore, the allergic reaction had to be a response to one of the components of the preparation (midazolam HCl, sodium chloride, disodium edetate, or benzyl alcohol) or its metabolites, as has been previously reported.⁴ Of interest is that other benzodiazepines, such as chlordiazepoxide, diazepam, and flurazepam, also have had reported allergies.⁴

The present report is most significant since, to the best of the authors' knowledge, there have been no reported allergic reactions to midazolam in a pediatric dental environment. Previously, reported allergic reactions to midazolam included a case of IV administration to a 38-year-old man undergoing cervical spine fusion and under general anesthesia that produced an anaphylactoid reaction.⁵ Another reaction was reported in a 34-year-old female who was sedated for an endoscopy.⁴ In any case, whenever a medication with the potential to create an allergic reaction is utilized, the dentist should be aware of its possible development, and be able to recognize and treat it.

Conclusions

1. Intranasal midazolam administered for pediatric conscious sedation in the dental office may induce an

allergic reaction, which should be recognized and treated as soon as possible.

2. Children who receive sedatives in the dental clinic should be carefully monitored from the moment they receive the sedative agent, in order to disclose and treat undesired side effects as early as possible.

References

1. American Academy of Pediatric Dentistry: Guidelines for the elective use of conscious sedation, deep sedation, and general anesthesia in pediatric dental patients. *Pediatr Dent. Reference Manual* 2001-02. 2002;23:73-79.
2. Waisbren BA, Smith MB. Hypersensitivity to meperidine. *JAMA*. 1978;239:1395.
3. Levy JH, Rockoff MA. Anaphylaxis to meperidine. *Anesth Analg*. 1982;61:301-303.
4. Yakel DL, Whittaker SE, Elstad MR. Midazolam-induced angioedema and bronchioconstriction. *Crit Care Med*. 1992;20:307-308.
5. Fujita Y, Ishikawa H, Yokota K. Anaphylactoid reaction to midazolam. Letter to the editor. *Anesth Analg*. 1994;79:811.
6. Nordt SP, Clark RF. Midazolam: A review of therapeutic uses and toxicity. *J Emerg Med*. 1997;15:357-365.
7. Anibarro B, Vila C, Seoane FJ. Urticaria induced by meperidine allergy. *Allergy*. 2000;55:305-306.
8. Houpt M. Project USAP 2000—Use of sedative agents by pediatric dentists: A 15-year follow-up survey. *Pediatr Dent*. 2002;24:289-294.
9. Malamed SF. Oral Sedation. Chloral derivatives. Chloral hydrate. In: Malamed SF, ed. *Sedation. A Guide to Patient Management*. 3rd ed. St. Louis:CV Mosby Co; 1995:114.
10. Midazolam hydrochloride injection [package insert]. Schaumburg, Ill. American Pharmaceutical Partners; 2002.
11. Meperidine hydrochloride injection [package insert]. Deerfield, Ill. Baxter Healthcare Corporation; 2001.
12. Kupietzky A, Houpt MI. Midazolam: A review of its use for conscious sedation of children. *Pediatr Dent*. 1993;15:237-241.
13. Hartgraves PM, Primosch RE. An evaluation of oral and nasal midazolam for pediatric dental sedation. *J Dent Child*. 1994;61:175-181.
14. Fukuta O, Braham RL, Yanase H, Kurosu, K. The sedative effects of intranasal midazolam administration in the dental treatment of patients with mental disabilities. Part 2: Optimal concentration of intranasal midazolam. *J Clin Pediatr Dent*. 1994;18:259-265.
15. Lejus C, Renaudin M, Testa S, Malinovsky JM, Vigier T, Souron R. Midazolam for premedication in children: Nasal versus rectal administration. *Eur J Anaesthesiol*. 1997;14:244-249.
16. Fukuta O, Braham RL, Yanase H, Kurosu K. Intranasal administration of midazolam: Pharmacokinetic and pharmacodynamic properties and sedative potential. *J Dent Child*. 1997;64:89-98.
17. Geldner G, Hubmann M, Knoll R, Jacobi K. Comparison between three transmucosal routes of administration of midazolam in children. *Paediatr Anaesth*. 1997;7:103-109.
18. Griffith N, Howell S, Mason DG. Intranasal midazolam for premedication of children undergoing day-case anesthesia: Comparison of two delivery systems with assessment of intraobserver variability. *Br J Anaesth*. 1998;81:865-869.
19. Henry RJ, Ruano N, Casto D, Wolf, RH. A pharmacokinetic study of midazolam in dogs: Nasal versus atomizer administration. *Pediatr Dent*. 1998;20:321-326.
20. Wilson S, Easton J, Lamb K, Orchardson R, Casamassimo P. A retrospective study of chloral hydrate, meperidine, hydroxyzine, and midazolam regimens used to sedate children for dental care. *Pediatr Dent*. 2000; 22:107-112.
21. Lloyd CJ, Alredy T, Lowry, JC. Intranasal midazolam as an alternative to general anesthesia in the management of children with oral and maxillofacial trauma. *Br J Oral Maxillofac Surg*. 2000;38:593-595.
22. Ljungman G, Krueger A, Andreasson S, Gordh T, Sorensem S. Midazolam nasal spray reduces procedural anxiety in children. *Pediatrics*. 2000;105:73-78.
23. Erlandsson AL. Backman, B, Stenstrom A, Stecksens-Blicks C. Conscious sedation by oral administration of midazolam in pediatric dental treatment. *Swed Dent J*. 2001; 25:97-104.
24. Primosch R, Bender F. Factors associated with administration route when using midazolam for pediatric conscious sedation. *J Dent Child*. 2001;68:233-638.
25. Dallman JA, Igelzi MA Jr, Briskie DM. Comparing the safety, efficacy and recovery of intranasal midazolam versus oral chloral hydrate and promethazine. *Pediatr Dent*. 2001;23:424-430.
26. Singh N, Pandey RK, Saksena AK, Jaiswal JN. A comparative evaluation of oral midazolam with other sedatives as premedication in pediatric dentistry. *J Clin Pediatr Dent*. 2002;26:161-164.
27. Walbergh EJ, Willis RJ, Eckhert, J. Plasma concentrations of midazolam in children following intranasal administration. *Anesthesiology*. 1991;74:233-235.
28. Fasel T, Hack, Knoll CR, Kraus GB, Larsen R. Nasal midazolam in children, plasma concentrations and the effect on respiration. *Paediatr Anaesth*. 1995;5:347-353.
29. Burstein AH, Modica R, Hatton M, Gengo FM. Intranasal midazolam plasma concentration profile and its effect on anxiety associated with dental procedures. *Anesth Prog*. 1996;43:52-57.
30. Hood LE, Weissman IL, Wood WB, Wilson JH. *The Immune System. Immunology*, 2nd ed. Menlo Park, Calif: The Benjamin/Cummings Publishing Company, Inc; 1984:1-15.
31. Nainar SM. Dental management of children with latex allergy. *Int J Paediatr Dent*. 2001;11:322-326.
32. Brown RS, Paluoi S, Choksi S, et al. Evaluating a dental patient for local anesthesia allergy. *Compend Contin Educ Dent*. 2002;23:125-128,131-132,134.