JPPT | Case Report

An Unusual Case of Delayed Midazolam Anaphylaxis and a Review of the Current Literature

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Midazolam is a commonly used, well-tolerated, anxiolytic, sedative, anesthesia induction agent, and an adjunct for procedural sedation that is used widely in the emergency department. The ability to administer midazolam via multiple routes, including intranasal, makes it a particularly common choice for use in children. Intranasal administration is safe, easy, and well tolerated and has been shown to be an effective method of obtaining anxiolysis and/or sedation. Adverse drug reactions, including allergic reactions, can occur with any medication. However, anaphylaxis is an uncommon phenomenon from midazolam. Despite being one of the most common medications used in the emergency department and operating room, there are only a handful of unequivocal cases of anaphylaxis secondary to midazolam. The rarity of this presentation may lead to delays in care and potential adverse outcomes as a result. We present one such case of a 10-year-old patient who experienced anaphylaxis after administration of intranasal midazolam to facilitate a computed tomography scan.

ABBREVIATIONS ADE, adverse drug event; CT, computed tomography; IM, intramuscular; IN, intranasal; IV, intravenous

KEYWORDS anaphylaxis; conscious sedation; hypnotics and sedatives; midazolam

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Introduction

Midazolam is a short-acting benzodiazepine medication commonly used as an anxiolytic, sedative, anesthesia induction agent, and adjunct for procedural sedation. Its use is particularly common in children. Intranasal (IN) administration is a safe, easy, and well-tolerated route of administration for procedural sedation.[1,2]

Anaphylaxis is considered to be a rare adverse effect of midazolam administration. The first documented reaction was in 1994, 9 years after the widespread introduction of the medication to the market.[3] In this case, a 38-year-old man with multiple medication allergies experienced an anaphylactoid reaction during surgery after midazolam administration. He experienced life-threatening hypotension, diffuse rash, and some facial edema without wheezing. Symptoms resolved after standard therapy of epinephrine, steroids, and antihistamines.[4] Although this was the first documented case and it was attributed to midazolam by timing, the patient had received multiple other medications. To this day, there remain only 10 to 20 well-documented cases of anaphylaxis attributable to midazolam.

Anaphylaxis due to medications is a well-documented phenomenon. This is a particularly well-studied area regarding occurrence during anesthesia.[3,5,6] Of note, there are regional differences in patterns of drug anaphylaxis that are to date not fully understood or elucidated. In the United States, antibiotics are the most associated with anaphylaxis. In Europe, neuromuscular blockers have a larger association with anaphylaxis.[5,7–9] Most cases to date of anaphylaxis secondary to midazolam have been documented in India, Korea, Japan, and Turkey, although isolated cases in Europe and the United States have been documented in recent years.[3]

Because of the use of midazolam for procedural sedation and induction of anesthesia, most documented cases present a complex history involving patients receiving multiple medications also known to cause anaphylaxis such as antibiotics and neuromuscular blockers. There remain only a handful of cases of midazolam anaphylaxis documented outside of the operating room.[10–12] This is a known challenge with identifying a causative agent and may result in reduced confirmation of anaphylaxis due to induction agents.[3,9] Previously published literature suggests that 52.6% of the time the causative agent could not be identified in perioperative anaphylaxis.[6] We present the first documented case of anaphylaxis secondary to IN midazolam. By highlighting midazolam as a possible cause of anaphylaxis we hope to raise the index of suspicion and reduce the likelihood of a missed adverse drug event (ADE).

Case Report

We present a 10-year-old, 20-kg, Hispanic female who presented for a fall down 10 stairs. Patient had a history significant for Sturge-Weber syndrome as well as Klippel-Trenauny and epilepsy. She had intellectual disability, port wine stain, glaucoma, cataracts, and a limb length discrepancy and vascular anomaly of the left meningeal blood vessels. She was able to walk at baseline but has some difficulty. The patient's home medications were cetirizine for seasonal allergies and levetiracetam for epilepsy. Patient had a documented history of rash with penicillin and anaphylaxis from lansoprazole. Of note, the patient was compliant with her levetiracetam, and her last seizure was more than 3.5 years prior to this event. She was brought to the ED for evaluation of possible head injury. Because of her limited ability to communicate at baseline, it was determined that a computed tomography (CT) scan of the head was necessary to assess for possible cervical spine, skull, or brain injury. The possibility of a period of observation as an inpatient was discussed but trauma surgery stated they would be unable to admit the patient without head imaging. She had previously undergone scans to evaluate her brain given her Sturge-Weber and had required procedural sedation for CT scans in the past. It was unclear if she had previously received midazolam. Her chart indicated she had received it, but her mother, who was extremely reliable, was adamant that she had never been given a benzodiazepine in the past. Pediatric emergency pharmacy was queried regarding a midazolam dose given complex medical history. The decision was made to administer midazolam 10 mg (0.5 mg/kg) IN (5 mg/mL; Pfizer, New York, NY).

Eleven minutes after administration of the midazolam, the patient's mother called for her nurse and requested physician evaluation for possible facial swelling. Because of the characteristic facies of her Sturge-Weber, there was initial difficulty in determining the presence of facial swelling or erythema. After an additional 2 to 3 minutes, an attending physician was brought to bedside for a second opinion. Upon reassessment the patient's condition had visibly worsened and she had a protruding tongue, edema to bilateral lips, and urticaria diffusely across the body. Patient had a dry cough and indicated discomfort in her throat as well as her abdomen. Patient was subsequently given intramuscular (IM) epinephrine. Given the rarity of both the patient's underlying condition as well as anaphylaxis to midazolam, the pediatric emergency pharmacist was called to bedside for recommendations regarding additional treatment and possible alternative causes. Patient initially experienced some relief, but the decision was made to give a second dose of epinephrine (see Table for a timeline of medication administration). On his review of past medication administration record and his discussions with the patient's mother, the pharmacist determined that no other medications or intravenous (IV) fluids were administered during her hospital stay and no home medications were given in the preceding 12 hours prior to the reaction. The patient was additionally given methylprednisolone, diphenhydramine, and ondansetron (see Table for dose and time stamps). Patient experienced complete resolution of objective signs and was resting comfortably upon completion of her trauma workup. Patient had been observed for approximately 5 hours after her ADE at time of discharge home with detailed return precautions.

Table. Medication Administration Record for the Case*

Medication	Route	Dose, mg	Time
Midazolam	IN	10	20:09
Epinephrine	IM	0.15	20:30
Diphenhydramine	IV	20	20:30
Methylprednisolone	IV	40	20:33
Ondansetron	IV	2	20:35
Epinephrine	IM	0.15	20:38

IM, intramuscular; IN, intranasal; IV, intravenous

* This table documents the medication, route, dose, and time at which medications were administered. These data are copied directly from the time-stamped medication administration record in the chart.

Discussion

We present one of the first unequivocal cases of anaphylaxis caused by administration of midazolam. Additionally, we believe this represents the first documented case of anaphylaxis from IN midazolam. Most cases of anaphylaxis after administration of midazolam document onset of symptoms within 2 minutes. When administered IV, midazolam has peak plasma concentration, and effect, in 30 to 60 seconds as compared with peak concentration at 1 hour for oral and 9 to 10 minutes for IN.[2,13] A single documented case of IM-administered midazolam resulting in anaphylaxis was also identified in the literature.[14] The 59-year-old man had no previous history of medication allergies but did receive multiple medications preoperatively. He experienced pruritis, and rash and angioedema were noted by physicians. No wheezing was reported. He also had documented hypotension after delayed administration of epinephrine. Symptoms resolved with epinephrine, steroids, and antihistamines.

This case demonstrated delayed symptoms of anaphylaxis, similarly to the case we present, in a patient who received midazolam prior to surgery.[14] He had previously received IV midazolam once during a prior surgery without issue. Administration methods with delayed onset of action, such as oral, IM, and IN, can make it more difficult to identify the causative agent.[15]

Immediate reactions are likely to be detected more readily because of heightened awareness immediately after injection.

Just 3 previously documented cases were found that demonstrated anaphylaxis after exposure to midazolam as a single agent.[10,16,17] In most documented cases, the patient received a number of medications (including midazolam for induction with subsequent general anesthesia), and analysis, or allergy testing after the fact, demonstrated that midazolam was likely a contributing factor. In one of the largest published case series, children underwent allergy testing after perioperative anaphylactic reactions. Some children tested positive for allergies to multiple medications, and others tested negative for all medication allergies, including those administered at the time of anaphylaxis.[7] Further complicating matters, there are some data that midazolam may have the potential for direct release of histamine. This means that interpretation of allergy testing may be complex and that there is a possibility of anaphylactoid reaction as well as anaphylactic.[7]

One small study of patients who presented to a drug allergy center in the United States after suspected medication-induced anaphylaxis implicated midazolam in 13.6% of patients. However, this study relied on skin testing, which has complications, as documented above.[18] This does, however, suggest that it is important to draw attention to midazolam as a possible cause of anaphylaxis. The limited documentation of anaphylactic and anaphylactoid reactions due to midazolam has the potential to lead to patient harm because even experienced physicians and pharmacists may fail to recognize what is currently considered a medical "zebra." The 2019 European position paper on the subject of perioperative hypersensitivity reactions did not mention midazolam as a possible causative agent.[9] Similarly, the definitive paper on allergic reactions in pediatric periprocedural sedation found that 21% of allergic reactions around sedation are the result of midazolam—but it did not find a single case of anaphylaxis.[19]

The Naranjo algorithm is a formula that identifies the likelihood that a reaction is related to administration of a drug. It was applied to assess the likelihood that our patient's reaction was caused by administration of midazolam achieving a score of 7 (see Supplemental Table).[20] We suspect the score would be higher, but the patient had never—and has not since—received the medication, the life-threatening nature made a placebo challenge unsafe and unethical, and likewise there was no dose adjustment made. As such, although a Naranjo score of 7 is "probable" for a drug reaction—in this case, anaphylaxis or anaphylactoid reaction—we believe that this definitively represents an ADE.[20] Review of the specific formulation used in this patient (5 mg/mL; Pfizer) demonstrated that there were no preservatives or excipients likely to cause an allergic reaction (sodium chloride, hydrochloric acid, sodium hydroxide).[21]

Conclusions

Anaphylaxis secondary to midazolam is a rare and poorly studied phenomenon. It is likely that underrecognition is a serious problem. Raising the index of suspicion for this ADE is likely to improve recognition and potentially reduce adverse patient outcomes.

Article Information

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