

A 2-year-old girl with periprocedural anaphylaxis

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ABSTRACT

Periprocedural or perioperative anaphylaxis is rare, with an estimated incidence of 1 in 10,000 to 40,000 sedation cases. During such procedures, patients are often exposed to numerous medications, such as antimicrobials, neuromuscular blocking agents, sedative and/or hypnotics, and opioids. The most commonly implicated agents include antibiotics (in the United States) and neuromuscular blocking agents (in Europe). In this article, we explore the differential diagnosis and laboratory investigation of a case of periprocedural anaphylaxis.

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CHIEF CONCERN

Anaphylaxis.

HISTORY OF THE PRESENT ILLNESS

A previously healthy 2-year-old girl presented to the allergy clinic for evaluation of periprocedural anaphylaxis. Two months earlier, she presented to the emergency department of a free-standing tertiary children's hospital for traumatic partial amputation of her left fifth phalanx. Due to her young age and nature of the injury, a decision was made to proceed with intravenous (IV) ketamine for procedural moderate sedation for repair. She received weight-appropriate doses of 124 mg of oral ibuprofen, and 0.02 mg of subcutaneous 1% lidocaine for IV placement, followed by 300 mg of IV cefazolin. Two hours later, she was given 18 mg of IV ketamine (1.5 mg/kg) for conscious sedation, and a digital block was performed with 50 mg of intradermal (ID) 1% lidocaine, after preparation with povidone-iodine 10%. Five minutes later, she developed a blanching, erythematous rash to her face and torso, followed by retching, coughing without stridor, and precipitous oxygen desaturation and facial cyanosis, with normal blood pressure and perfusion.

She was immediately repositioned and ventilated with oxygen *via* a bag-valve mask, and given 0.12 mg of intramuscular epinephrine, 12.5 mg of IV methylprednisolone, and 10 mg of IV diphenhydramine. She received nebulized albuterol for persistent coughing. After 3 minutes, she had normalization of her oxygen saturations and full resolution of her symptoms. She continued to be asymptomatic 1 hour after the onset of symptoms, and nailed repair was successfully completed. She was observed for 4 hours after complete resolution of her symptoms and was discharged from the emergency department with prescriptions for an epinephrine autoinjector, prednisolone, and diphenhydramine. Before discharge, her caretakers completed training with a clinical pharmacist on the use of the epinephrine autoinjector and were instructed with regard to signs and symptoms of recurrent reactions. She was referred to our allergy clinic for further evaluation.

The patient had no history of similar reactions to any medications, foods, or insect stings. She had not had any previous surgical or dental procedures, and no previous exposure to any sedatives or systemic anesthetics. Topical lidocaine was used for her in the past at the site of mosquito bites, without adverse reaction. Amoxicillin was also used for her on two occasions for ear infections. Her mother reported that a few days after starting the second amoxicillin course, the patient developed a scattered nonpruritic papular rash on her arms, with no other associated symptoms. She did not have a history of atopic disease, including asthma, atopic dermatitis, or food allergy.

PHYSICAL EXAMINATION DOCUMENTED IN THE EMERGENCY DEPARTMENT

She was well appearing, with an unremarkable pre-procedural physical examination, including an

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Table 1 SPT and ID testing results

Antigen	SPT	ID Test	
	Wheal/Flare, mm	Initial Wheal, mm	Wheal at 15 min, mm
Histamine	6/23		
Saline solution	0/0	5	0
Cefazolin, 33-mg/mL ID test		5	6
Ketamine, 10-mg/mL SPT, 1-mg/mL ID test	0/0	4	11
Lidocaine, 0.1%	4/0	5	0

SPT = Skin-prick test; ID = intradermal.

unobstructed airway. Her left hand was supported in a splint.

QUESTIONS

What Is the Differential Diagnosis?

The rapid onset of cutaneous and respiratory symptoms during sedation is most consistent with the diagnosis of anaphylaxis. Given the timing, possible inciting agents include ketamine, lidocaine, and cefazolin. Other considerations due to ketamine include acute laryngospasm; however, laryngospasm typically causes stridor and is not associated with hives.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

To further evaluate for the inciting agent, we pursued skin testing to the possible culprit agents. Given the patient's age, we attempted to minimize the number of skin-prick tests (SPT) and ID tests. Because we had the highest suspicion for ketamine or lidocaine as the causative agent, we performed an SPT with 10 mg/mL of ketamine and 0.1% of lidocaine, with histamine and saline solution controls, followed by ID testing with highest concentration of 1 mg/mL of ketamine and 0.1% of lidocaine. We also performed ID testing for cefazolin.

DISCUSSION

The results of skin testing are summarized in Table 1. On SPT, there was an adequate histamine response (6-mm wheal), negative 10 mg/mL ketamine SPT result (0-mm wheal), and questionable positive 0.1% lidocaine SPT result (4-mm wheal with no flare). Given the lower clinical suspicion for lidocaine, we went ahead and performed the rest of the ID testing, including lidocaine. ID testing results were negative for 33 mg/mL of cefazolin, negative for 0.1% lidocaine, and positive ID for 1 mg/mL of ketamine (increase of 7 mm in wheal size in 15 minutes). To confirm our findings, we challenged her with an intramuscular 0.5-mL 1% lidocaine dose, which she tolerated without reactions. Her rash during a

previous amoxicillin course did not seem consistent with an immediate immunoglobulin E (IgE) mediated reaction, and she tolerated oral challenge to amoxicillin without reactions. Given the low clinical suspicion for cefazolin and negative ID testing results, we concluded that ketamine was likely the inciting agent. However, given that we did not challenge the patient to IV cefazolin, the first dose of future cefazolin dose should be administered with caution.

This case demonstrated an anaphylactic reaction, likely to ketamine. Perioperative or perioperative anaphylaxis is rare, with an estimated incidence of 1 in 10,000 to 40,000 sedation cases.^{1,2} Ketamine is widely used for procedural moderate sedation in the pediatric setting and overall is well tolerated.³ Allergic reactions to ketamine are rare; a recent retrospective analysis of the Pediatric Sedation Research Consortium¹ evaluated 227,833 sedation cases to define the incidence of allergic reactions during procedural sedation. Allergic reactions were defined as the development of urticaria, rash, breathing difficulty, angioedema temporally related to delivery of sedative. Anaphylaxis to any sedative and/or hypnotic agent was extremely rare; six cases of anaphylaxis were identified, five of which involved propofol, and no episodes were attributed to ketamine. There were 48 allergic reactions, with 16 reactions to ketamine of 18,333 sedation cases of patients who received ketamine.¹

Anaphylaxis to ketamine has been reported in case reports.⁴⁻⁶ However, the underlying mechanism by which ketamine induces mast cell degranulation is not entirely clear. There is evidence that some reactions may be nonimmunologic or anaphylactoid in nature. When using the Prausnitz-Kutzner test, Mathieu *et al.*⁷ took sera from a 3-year-old boy who had developed a rash in response to ketamine and transferred the sera *via* ID to two of the investigators. The investigators were then challenged with ID ketamine at the same sites, with a negative response, which suggested that this was not an IgE-mediated process.⁷ Stellato *et al.*⁸ demonstrated evidence that ketamine can directly lead to histamine release from mast cells *in vitro*, and there is significant heterogeneity in this effect across mast cells from different anatomic sites.

Similarly, in a cohort of patients with allergy, Kimura *et al.*⁹ found that increased histamine release occurred in approximately one-third of patients after receiving midazolam and ketamine. In contrast, Fujimoto *et al.*¹⁰ demonstrated that, in a canine mast cell model, ketamine decreased mast cell exocytosis in a dose-dependent manner. Serum tryptase has been reported in some cases⁶; however, serum tryptase is a nonspecific marker for mast cell degranulation and, as such, does not help to distinguish between immunologic and nonimmunologic mechanisms.¹¹ It is likely that both immunologic and nonimmunologic mechanisms play a role in mediating anaphylaxis to ketamine. At this point, a ketamine-specific IgE assay to further define this underlying mechanism in our patient is not available.

FINAL DIAGNOSIS

Anaphylaxis, likely secondary to ketamine.

CONCLUSION

Allergic reactions to hypnotic induction agents are rare, and anaphylaxis to ketamine is exceedingly rare. Although the underlying immunologic or nonimmunologic mechanism that mediates anaphylaxis may be uncertain, the treatment of the severe systemic symptoms secondary to mast cell degranulation is not. Prompt identification of anaphylaxis is crucial and demands administration of epinephrine as soon as possible.

REFERENCES

1. Hertzog JH, Preisberga K, Penfil S. The incidence and nature of allergic and anaphylactic reactions during pediatric procedural sedation: a report from the Pediatric Sedation Research Consortium. *Hosp Pediatr*. 2019; 9:16–23.
2. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015; 115:341–384.
3. Bellolio MF, Puls HA, Anderson JL, et al. Incidence of adverse events in paediatric procedural sedation in the emergency department: a systematic review and meta-analysis. *BMJ Open*. 2016; 6:e011384.
4. Bylund W, Delahanty L, Cooper M. The case of ketamine allergy. *Clin Pract Cases Emerg Med*. 2017; 1:323–325.
5. Ki S, Lim S, Kim MH, et al. Immediate hypersensitivity reaction to ketamine in children with history of atopic disease. *Asian Pac J Allergy Immunol*. 2018; 36:32–34.
6. Ozcan J, Nicholls K, Jones K. Immunoglobulin E-mediated hypersensitivity reaction to ketamine. *Pain Pract*. 2016; 16:E94–E98.
7. Mathieu A, Goudsouzian N, Snider MT. Reaction to ketamine: anaphylactoid or anaphylactic?. *Br J Anaesth*. 1975; 47:624–627.
8. Stellato C, Casolaro V, Ciccarelli A, et al. General anaesthetics induce only histamine release selectively from human mast cells. *Br J Anaesth*. 1991; 67:751–758.
9. Kimura K, Adachi M, Kubo K. H1- and H2-receptor antagonists prevent histamine release in allergic patients after the administration of midazolam-ketamine. A randomized controlled study. *Inflamm Res*. 1999; 48:128–132.
10. Fujimoto T, Nishiyama T, Hanaoka K. Inhibitory effects of intravenous anesthetics on mast cell function. *Anesth Analg*. 2005; 101:1054–1059.
11. Veien M, Szlam F, Holden JT, et al. Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. *Anesthesiology*. 2000; 92:1074–1081. □

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