



Midazolam and Ketamine Hypersensitivity in a Four Year Old Child

Dört Yaşındaki Bir Çocukta Midazolam ve Ketamin Hipersensitivitesi

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ABSTRACT

Hypersensitivity reactions during anesthesia are rarer in childhood when compared with adults. In both children and adults, neuromuscular blocking agents are the most frequently incriminated drugs in this setting followed by antibiotics. Benzodiazepines and ketamine are generally regarded as exceptional drugs regarding allergy. In this report, we present a 4-year old child who developed urticarial lesions during anesthesia and was found to have hypersensitivity to both midazolam and ketamine when diagnostic tests were performed.

Key words: Urticaria, anesthesia, midazolam, ketamine, hypersensitivity

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ÖZ

Çocuklarda anestezi sırasında görülen hipersensitivite reaksiyonları erişkinlere göre daha nadirdir. Nöromusküler bloke edici ajanlar hem erişkinlerde hem de çocuklarda anestezi sırasında en sık duyarlılık saptanan ajanlardır ve antibiyotik duyarlılığı bu ajanları takip etmektedir. Benzodiazepinler ve ketamin genellikle allerjinin çok da sık görülmediği ajanlar olarak bilinirler. Yazıda anestezi sırasında ürtikeryal lezyonları ortaya çıkan ve tanısal testler yapıldığında hem midazolam hem de ketamine duyarlılık saptanan 4 yaşında bir çocuk hasta sunulmuştur.

Anahtar kelimeler: Ürtiker, anestezi, midazolam ketamin, hipersensitivite

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INTRODUCTION

Hypersensitivity reactions in the anesthesia setting are rarer in childhood when compared with adults (1,2). In both children and adults, neuromuscular blocking agents are the most frequently incriminated drugs in this setting followed by antibiotics (2).

Benzodiazepines and ketamine are generally regarded as exceptional drugs regarding allergy (3). Midazolam is a short-acting benzodiazepine that is commonly used for sedation and premedication in children. Although respiratory depression and respiratory arrest have

been described, allergic reactions such as angioedema, bronchoconstriction and urticarial lesions have been reported in a few cases in the literature (4-7). Ketamine, a phencyclidine derivative, has been found to be a useful drug with its ease of administration and documented safety profile in anesthesia. It has also rarely been reported to cause allergic reactions like midazolam (8,9). In this report, we present a 4-year old child who had developed urticarial lesions after intravenous (IV) administration of midazolam. She was found to have hypersensitivity to both midazolam and ketamine when diagnostic tests were performed.

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CASE REPORT

A 4-year old girl was referred to our clinic for investigation of midazolam hypersensitivity after she experienced generalized urticarial lesions after IV administration of midazolam. She had been diagnosed with nephrolithiasis since two years of age and had received general anesthesia for four times including for nephrostomy catheter replacement, cystoscopic evaluations and lastly percutaneous nephrolithotripsy. She had experienced similar urticarial lesions during anesthesia six months before at a local hospital but details of the reaction and the drugs could not be obtained. She had not experienced any systemic symptoms during either episode. Her symptoms had been treated with IV antihistamine and IV prednisolone and the urticarial lesions had resolved. She had no history of asthma, allergic rhinitis or food allergy and had no known reactions to other drugs including antibiotics. Six weeks after the last reaction, she was evaluated with the prick and intradermal tests of midazolam and other anesthetics to be used in the following procedure. Midazolam, ketamine, propofol, fentanyl, rocuronium and thiopental were tested at final concentrations of 5 mg/ml, 10 mg/ml, 10 mg/ml, 0.05 mg/ml, 10 mg/ml and 25 mg/ml (12). Dilutions up to 1/10 were used for intradermal testing. Intradermal tests were positive for midazolam and ketamine at 1/10 concentration and no hypersensitivity was detected for other drugs (Figure 1). Skin prick testing for latex was negative and specific IgE for latex was unremarkable.



Figure 1. Positive intradermal test with midazolam.

DISCUSSION

Adverse drug reactions have been recognized as one of the most common causes of morbidity and death in anesthesiology practice (1). However, allergic reactions in the anesthesia setting are usually harder to interpret because reactions are usually regarded as toxic, pharmacologic and anesthetic rather than allergic. Medications are given sequentially and quickly, which also makes difficult to determine the real causative agent. Presentation of an allergic reaction can be confused with other causes of hypotension and respiratory compromise, and draping may also prevent detection of skin lesions such as urticaria and angioedema. Therefore suspicion is the most important thing in diagnosing allergic reactions to anesthetic drugs and enables referral of the patient to the allergy clinic.

Midazolam and ketamine are generally regarded as safe drugs and are commonly used in pediatric practice. However, there are several reports showing that allergic reactions ranging from mild urticarial lesions to anaphylaxis can be observed with these drugs (4-9). Our patient who had a clear-cut urticarial reaction after IV administration of midazolam was treated immediately with antihistamines and steroids and did not develop any systemic reactions. The previous reaction of our patient was probably due to midazolam but we cannot exclude a reaction to ketamine because ketamine hypersensitivity was also diagnosed by intradermal testing. There are three cases of anaphylactoid reactions in the literature which were reported to follow IV administration of midazolam. The first patient, a 26-year old female, developed facial edema and pruritus after administration of midazolam but systemic reactions were not noted (10). In another case, midazolam induced angioedema and bronchoconstriction (4). The last patient was a 38-year old male who was allergic to several antibiotics and developed hypotension after administration of midazolam (6). There are four children in the literature reported to develop mild allergic reactions to nasal midazolam (5,7). None of these patients were tested with skin tests to midazolam. Our patient is the first pediatric case developing allergic reactions after administration of IV midazolam that was also confirmed by skin testing. Allergic reactions to ketamine have been described in three reports. They are all pediatric cases ranging from rashes to anaphylaxis (8,9,11). The first patient, a 3-year old child, developed an extensive macular rash attributed to the direct pharmacological effect of the

drug rather than an allergy (8). The second patient was a 2.5 year old child who developed severe respiratory failure and urticarial lesions after administration of IV ketamine (9). The third patient was a 6-year old female who developed urticarial lesions and wheezing after administration of midazolam and ketamine and investigations revealed a positive reaction to ketamine.

Skin tests coupled with history remain the mainstay of the diagnosis of IgE-mediated drug reactions. Tests are generally performed 4-6 weeks after the reaction. The perioperative drug skin concentrations recommended have been recently reported (12). We performed all potential anesthetic drugs that were or could have been used in our case and found no sensitivity to latex, propofol, fentanyl, rocuronium and thiopental. We did not perform tests with antibiotics because she had no history of any adverse reactions to a wide spectrum of antibiotics.

In conclusion, we presented this case to emphasize the potential of allergic reactions to midazolam and ketamine in children. Anesthetists should be careful when administering midazolam and ketamine that are generally regarded as safe and well tolerated and refer the patients to allergy clinics if there is a suspicion of an allergic reaction.

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