Received Date : 14-Nov-2015

Revised Date : 10-Mar-2016

Accepted Date : 21-Mar-2016

Article type : Case Report

Immunoglobulin E-Mediated Hypersensitivity Reaction to Ketamine

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Article type: CLINICAL REPORT

Key Words: ketamine; allergy; hypersensitivity; IgE-mediated

Running title: IgE-Mediated Hypersensitivity to Ketamine

Submitted: November 14, 2015; Revision accepted: March 21, 2016

Conflicts of Interest

None.

Abstract

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/papr.12466](https://doi.org/10.1111/papr.12466)

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Introduction

Ketamine is a commonly used analgesic agent in the management of both acute and chronic pain. While dose-dependent side effects are well described, allergy to ketamine is extremely rare.

Case

A 41-year-old woman with chronic pelvic pain and previous ketamine exposure developed a widespread urticarial rash and mild perioral edema following the initiation of a ketamine infusion. The infusion was ceased and the patient was treated with oral antihistamine, with rapid resolution of symptoms. Serum tryptase levels were elevated at 2 and 6 hours after the infusion was ceased, and subsequent intradermal skin testing supported the diagnosis of type I hypersensitivity reaction to ketamine.

Discussion

This case represents a likely immunoglobulin E-mediated type I hypersensitivity reaction to ketamine, supported by elevated tryptase levels and positive intradermal skin testing. The interpretation of these results and likely mechanism of the hypersensitivity reaction are described. The patient and treating team were advised against subsequent use of ketamine, due to the risk of serious adverse systemic reaction with repeat exposure.

Introduction

Ketamine, a phencyclidine derivative, has been in use for more than 50 years, initially as a dissociative anesthetic agent but more recently as an analgesic and antihyperalgesic agent in acute and chronic pain. Its mechanism of analgesic action is complex, and mediated via multiple receptors in both the central and peripheral nervous systems. Immediate effects are receptor mediated, including noncompetitive blockade of *N*-methyl-D-aspartate (NMDA) receptors, reducing presynaptic release glutamate. Ketamine also interacts with multiple other receptors, including opioid, monoaminergic, nicotinic, and muscarinic cholinergic receptors, as well as voltage-dependent ion channels.^{1,2} Delayed and longer lasting effects of ketamine are mediated via alteration in gene expression and protein regulation.¹ Side effects to ketamine occur typically in a dose-dependent fashion. The most common are nausea and vomiting, hallucinations, dysphoria, bizarre dreams, and emergence delirium.

Immediate hypersensitivity reaction to ketamine is rare, and despite the drug's long history and widespread use, case reports in the literature are scant.³⁻⁶ Ketamine reaction with an associated rise in serum tryptase has not been previously reported. Two previous reports of

ketamine allergy confirmed by skin testing have been published. Karayan et al. reported an allergy to ketamine in the form of generalized rash and laryngospasm.³ The patient underwent intradermal skin testing 2 years after the event, with positive responses to ketamine at dilutions of 10^{-1} (10 mg/mL) and 10^{-2} (1 mg/mL). Boynes et al. described a 6-year-old girl developing a severe urticarial reaction following administration of intramuscular ketamine and midazolam prior to a dental procedure.⁴ The patient developed an urticarial rash involving the neck, back, and torso, and wheeze on auscultation. Vital signs remained stable, and the rash and wheeze resolved following administration of diphenhydramine. It is reported that further investigation confirmed positive reaction to ketamine, but the details of this testing are not described. Ketamine's product information states that anaphylaxis has been observed, and that transient erythema and rash have been reported, but few details are provided.⁷

Adverse drug reactions are noxious and unintended responses to a drug that occur at doses normally used in humans and can be classified as type A or type B reactions.⁸ Type A reactions are due to augmented pharmacological properties of the drug. They are dose dependent and occur on exposure in most individuals at high enough doses. Examples with ketamine are nausea and vomiting, dysphoria, and hallucinations. Type B reactions are idiosyncratic and non-dose dependent, occur only in predisposed individuals, and are harder to predict. Type B reactions are also known as drug hypersensitivity reactions and may have immune-mediated or nonimmune mechanisms. Drug allergy by definition is an immune-mediated hypersensitivity reaction.⁹

We present the case of a 41-year-old woman with a likely immunoglobulin E (IgE)-mediated type I hypersensitivity to ketamine. The patient developed a widespread urticarial rash and mild perioral edema during the administration of a ketamine infusion for management of chronic pelvic pain. Serum tryptase levels were elevated at 2 and 6 hours after the infusion was ceased, and subsequent intradermal skin testing supported the diagnosis of ketamine hypersensitivity reaction.

Case Report

A 41-year-old nulliparous woman with chronic pelvic pain was electively admitted for ketamine infusion for pain management, after having previous treatments with ketamine with good effect. She had experienced daily episodes of abdominopelvic pain for more than 10 years. Previous interventions included a laparotomy to investigate an episode of acute pelvic pain, at which pelvic inflammatory disease was diagnosed. This was followed by a left ectopic pregnancy and right hydrosalpinx requiring bilateral salpingectomy. The patient

subsequently had multiple laparoscopies to investigate her pain, during which pelvic adhesions and minimal endometriosis were found, and adhesiolysis was performed. She also had multiple attempts at in vitro fertilization without success.

At the time of admission her medications were estradiol 2 mg/dydrogesterone 10 mg once daily and topical estradiol gel for perimenopausal hormone replacement therapy, and pramipexole 0.25 mg daily as needed for restless legs syndrome. The patient had no known drug or food allergies, and no history of asthma, eczema, or allergic rhinitis. She was a current tobacco smoker (10 cigarettes/day) and had a history of previous marijuana use, but no other illicit drug use.

The patient had tried a number of medications, including gabapentin, nortriptyline, clonidine, and tramadol, each with limited improvements in her pain. Previous trials of the oral contraceptive pill and mefenamic acid also provided little change in her pain. Her current analgesic regimen was paracetamol 500 mg/codeine 30 mg on an as-needed basis, requiring 2 to 6 tablets per day. She had had 4 previous admissions for elective ketamine infusion over the previous 4 years. Each admission was for a period of 5 to 7 days, with continuous ketamine infusion titrated up to 16 mg/hour. Each of these was associated with significant improvement in the patient's symptoms such that she required no codeine-containing preparations for up to 6 months after the ketamine infusion. She reported that avoiding the sedative side effects of analgesics made it easier and safer to perform her occupation as a window cleaner.

On the day of admission the patient's regular medications were charted, with the addition of gabapentin 300 mg at bedtime to treat for restless legs syndrome, and temazepam 10 mg for insomnia. The patient had used each of these medications previously, and both were given on the evening of admission. Ketamine was commenced at 12 mg/hour continuous infusion with no initial bolus. The infusion consisted of 200 mg ketamine in 50 mL normal saline (4 mg/mL ketamine). The following day, after 20 hours of the infusion at 12 mg/hour, the patient became nauseated and vomited, and developed a small area of itchy urticarial rash on the anterior chest wall. The ketamine infusion was stopped, intravenous ondansetron 4 mg and oral promethazine 10 mg were administered, and the nausea and rash both resolved over the next hour. The ketamine infusion was restarted 2 hours later. Within 1 hour of restarting the infusion, the patient developed a widespread urticarial rash involving the abdomen, chest wall, and neck. She also complained of anterior chest pain that was pleuritic in nature. Some minor perioral edema was evident, but there was no stridor, wheeze, or respiratory compromise. Oxygen saturations remained 99% in room air, and blood

pressure was stable at 130/60 mm Hg. Electrocardiography showed a sinus rhythm with a rate of 72 beats per minute. The ketamine infusion was ceased immediately and the patient was treated with oral loratadine 10 mg, with resolution of the rash within 1 hour.

Ketamine allergy was suspected given the temporal relationship of the reactions to ketamine administration. Blood samples were taken, and further ketamine administration was withheld. The patient remained in hospital overnight without further incident, then was discharged home the following day on her usual analgesic regimen with a plan for outpatient pain clinic follow-up.

Serial blood samples for serum tryptase were collected and were found to be elevated at 25.7 µg/L (reference range <11.5 µg/L) at 2 hours and 12.3 µg/L at 6 hours after the episode. Results of full blood examination, urea and electrolytes, creatinine, estimated glomerular filtration rate, and liver function tests were all within normal ranges. There were no clinical features to suggest systemic mastocytosis.

The patient was referred for allergy testing to a member of the Australia and New Zealand Anaesthetic Allergy Group (ANZAAG), an Australasian network of specialist anesthesiologists, immunologists, and allergists with interest and expertise in perioperative allergy, for consideration for further testing. The case was discussed at a meeting of the group, who, given the patient's desire for ongoing treatment with ketamine, agreed that testing would be appropriate. Skin testing took place 12 weeks after the reaction. Intradermal skin testing was conducted, revealing a positive reaction to ketamine at a concentration of 1 mg/mL and 0.1 mg/mL (Table 1).

The case was also reviewed by the adverse drug reaction committee of the hospital. A detailed explanation of the serious nature of the hypersensitivity was provided to the patient, and she was advised against further treatment with ketamine. The potential for major systemic reaction and anaphylaxis with any future administration was explained. The allergy was documented in her medical records and written notification given to her general practitioner.

Discussion

Immediate hypersensitivity drug reactions, including anaphylaxis, have been reported for nearly all drug classes.¹⁰ These reactions can progress rapidly, with severity ranging from minor dermatological changes to catastrophic and potentially fatal cardiovascular collapse. The mechanism of hypersensitivity can be immune mediated or occur via nonimmune mechanisms. Immune-mediated hypersensitivity reactions confer increased risk for enhanced reactions on subsequent exposure due to immunologic memory.

Anaphylaxis is an IgE-mediated type I hypersensitivity reaction. It is a severe, life-threatening, systemic allergic reaction characterized by acute onset of illness with multisystem involvement, including skin, mucosal tissue, plus respiratory and/or cardiovascular compromise.¹¹ Nonimmune mechanisms can produce the same clinical picture as anaphylaxis, but are not IgE mediated, and were previously described as anaphylactoid reactions. The mechanism of nonimmune drug hypersensitivity involves a direct release of histamine from mast cells. An example of this effect is “red man syndrome” observed with vancomycin administration.¹⁰

The present case is consistent with an immune-mediated type I hypersensitivity reaction to ketamine. Raised serum tryptase levels are consistent with mast cell degranulation, and positive intradermal testing is suggestive of IgE-mediated allergy. In vitro tests for allergen-specific IgE in serum, which would be most definitive of an immune-mediated mechanism, are not presently available for ketamine. While this case did not present with life-threatening features such as airway or cardiovascular compromise, the presumed IgE-mediated mechanism for this reaction places the patient at risk for severe systemic reaction or anaphylaxis with future exposure to ketamine.

Risk factors for sensitization to a drug can be classified as drug-, treatment regimen-, and patient-related factors.^{12,13} Drug-related factors include chemical properties and molecular weight of the drug. Treatment regimen-related factors include pattern and route of administration. Intermittent and repeated administrations are more sensitizing than continuous drug use, and parenteral and epicutaneous routes of administration carry greater risk for sensitization compared to oral administration.¹³ Patient factors, such as coexisting viral infection or immunosuppression, can also increase the risk for sensitization. In the described case, there was no change in patient health status or concurrent illness at the time of the reaction. However the infrequent intermittent doses of intravenous ketamine she had previously received may have contributed to sensitization to the drug.

There have been no previous reports in the literature of ketamine allergy with elevated tryptase. While the clinical picture in the present case was not one of anaphylaxis, with lack of respiratory or cardiovascular compromise, tryptase levels were measured to complete a thorough profile of the reaction, given that exclusion of allergy would likely lead to trial of the agent again in the future.

Tryptase is the most abundant mediator stored in mast cell granules, and its release is characteristic of mast cell degranulation.¹⁴ Tryptase levels peak at 15 to 120 minutes, with a half-life of 90 to 250 minutes. The results in the present case were consistent with mast cell

degranulation, with tryptase levels maximally elevated at 2 hours after cessation of ketamine infusion and more mildly elevated at 6 hours. Increased serum tryptase levels are highly suggestive of an immune-mediated reaction but may also occur following direct mast cell activation and subsequent histamine release.^{14,15} Elevated serum tryptase in isolation does not provide definitive evidence of an IgE-mediated reaction, and further substantiation with skin testing is warranted.

Skin tests (prick and intradermal) represent an important diagnostic tool in the determination of IgE-mediated reactions. In the present case the patient was referred for allergy testing via the ANZAAG, and intradermal skin testing was positive for ketamine at concentrations of 1 mg/mL and 0.1 mg/mL (Table 1).

Intradermal tests are more sensitive and reproducible than the prick test, but they can be prone to false-positive results when too high a concentration is used, when the drug causes spontaneous local mast cell degranulation, or where negative and positive controls are absent.¹⁶ When high drug concentrations are used in intradermal testing, there is increased risk for producing an immediate reaction on the basis of nonspecific irritation of mast cells.¹⁶ Current guidelines¹⁷ report a maximum nonirritating concentration of ketamine for intradermal testing to be 1 mg/mL. An earlier study by Hagau and colleagues performed skin testing on healthy volunteers without allergy, and found the maximum nonreactive intradermal test concentration for ketamine to be 0.25 mg/mL.¹⁸ A positive reaction in the present case at a concentration of 0.1 mg/mL is therefore likely to be significant and highly suggestive of an IgE-mediated reaction.

Non-immune-mediated direct histamine release is a less likely mechanism in the present case, given the findings of elevated tryptase levels and positive intradermal testing. The literature is conflicting when trying to determine the capacity of ketamine to cause direct mast cell degranulation and histamine release. Some studies have demonstrated mast cell histamine release with ketamine use,¹⁹ although one such study was in a patient group with a history of allergy (asthma, hay fever, allergic rhinitis, atopic dermatitis).²⁰ Other studies have found that ketamine inhibits mast cell exocytosis and histamine release in animal models.²¹

Analgesic agent allergy presents a unique problem when compared to other anesthetic allergies whereby patients may be motivated to continue use of the agent. In the present case, the patient had previously had significant benefit from ketamine infusions, enabling her to manage without opioid analgesia for up to 6 months after treatment. Careful discussion with the patient about the implications of this allergy and risk for serious systemic reaction with further exposure was necessary to convince her that ketamine infusion should not be

repeated. Desensitization therapy could potentially be considered if there was no other suitable alternative agent available. While this has not been previously described in the literature for ketamine to our knowledge, there is good evidence as to the efficacy of desensitization regimens for IgE-mediated hypersensitivity.^{12,22}

Ketamine is a commonly used analgesic agent, and allergy to ketamine is extremely rare. We present a case of likely IgE-mediated hypersensitivity to ketamine, supported by elevated tryptase levels and positive intradermal skin testing. The patient and treating team were advised against subsequent use of ketamine due to the risk for serious systemic reaction.

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Table 1. Intradermal Skin Testing

Agent	Concentration	Response
Morphine (positive control)	0.1 mg/mL	7 × 7 mm
Ketamine	0.1 mg/mL	6 × 4 mm
Ketamine	1 mg/mL	10 × 8 mm
Normal saline (negative control)		No response
Chlorhexidine	2 µg/mL	No response

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Title:

Immunoglobulin E-Mediated Hypersensitivity Reaction to Ketamine

Date:

2016-09-01

Citation:

Ozcan, J., Nicholls, K. & Jones, K. (2016). Immunoglobulin E-Mediated Hypersensitivity Reaction to Ketamine. PAIN PRACTICE, 16 (7), pp.E94-E98. <https://doi.org/10.1111/papr.12466>.

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