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Case Report

A Case of Bradycardia and Hypersensitivity with Intravenous Ketamine Monotherapy

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Received date: January 25, 2021; Accepted date: February 13, 2021; Published date: February 20, 2021
Citation: Mishra P, Gupta B. and Parameswaran P., (2021) A case of bradycardia and hypersensitivity with intravenous ketamine monotherapy. *Clinical Medical Reviews and Reports* 3(2); DOI:10.31579/2690-8794/066

Abstract

Anaphylaxis during anesthesia is an unforeseeable and potentially life threatening syndrome that is dose independent. Ketamine is a widely used hypnotic for procedural sedation in the emergency department, in anesthesia and intensive care units (ICU). It is popularly employed for both children and adult patients. Though, dose dependent adverse effects of ketamine have been described, the hypersensitive reactions with the same are extremely rare. We are hereby presenting a case of an allergic reaction and isolated bradycardia with ketamine, given as intravenous monotherapy in a patient with no previous history of atopic disease. Our article aims at reminding all the medical professionals to never let a drug (however commonly used) throw away caution, be vigilant to timely diagnose an adverse drug reaction (even the most infrequent and rare) and be prepared to tackle the worst with the necessary supportive measures like hemodynamic support and advanced airway procedures.

Keywords: bradycardia; hypersensitivity; intravenous ketamine monotherapy

Background

The incidence of anaphylactic reactions during anesthesia ranges between 1 in 4000 to 1 in 25,000 and the mortality is estimated to be between 3 to 6% [1]. These are commonly seen with latex, neuromuscular blockers, opioids, antibiotics and blood transfusion etc. Though, dose dependent adverse effects of ketamine have been described, the hypersensitive reactions with the same are extremely rare. After taking informed consent for possible publication in literature, we are presenting such a rare case of intravenous ketamine allergy accompanied with bradycardia.

Case presentation

A 53 year old, 52 kg female patient was posted for incisional hernia repair under general anesthesia. She had an uneventful history of two caesarean section and one hernia surgery in the past. The anesthetic records of these surgeries were unavailable. Our anesthesia team was conducting a study regarding propofol induced pain in which intravenous (IV) ketamine was one of the test drugs. Post randomization, this patient was allocated to the ketamine receiving group. The study involved achieving venous stasis by inflating a tourniquet on the arm in which the selected drug would be given. Inside the operating room, the baseline vitals were recorded as heart rate (HR) - 62/min, Blood pressure – 106/64mm Hg and oxygen saturation (spO_2) of 99% on air. After securing venous access and tourniquet inflation at 100mm Hg, we began to give the sub-anesthetic dose of ketamine (15mg) IV. Patient immediately complained of burning sensation and itching over the forearm so further administration was stopped and tourniquet released. We noticed red macular spots that evolved into morbilliform, blanchable rash over the forearm and hand below the tourniquet. There was a transient fall in HR to 45/min that resolved spontaneously. However, there was no associated change in respiration or blood pressure. Suspecting an allergic reaction to the given drug, we gave inj. hydrocortisone 100 mg and inj. pheniramine 45.5 mg IV stat. This was followed by regression of rash. Patient was then induced and surgery commenced. Patient was extubated uneventfully at the end of procedure. However, still the rash had not resolved completely.

Investigations

Ketamine hypersensitivity test was done later by an intradermal injection of 1mg/ml ketamine both 2 days and 6 weeks after surgery.

Differential diagnosis

The possibility of these lesions being petechiae induced by the tourniquet was ruled out as they were blanchable and the coagulation profile and platelet count was normal in the patient.

Outcome and follow-up

While the control using normal saline was negative (Figure 1), redness with eruption of size 13 mm and 12 mm respectively at 2 days and 6 weeks with ketamine confirmed positive tests (Figure 2).

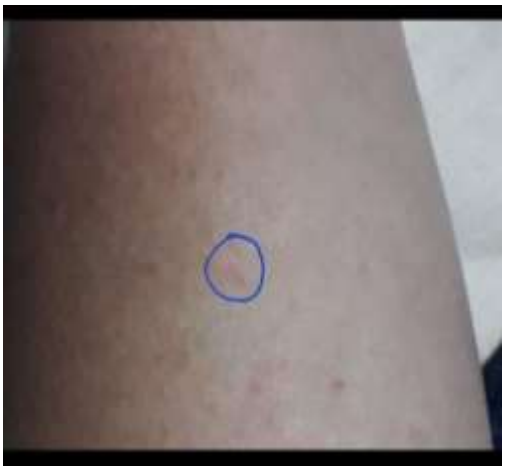

Figure 1. Intradermal test showing negative result with control normal saline

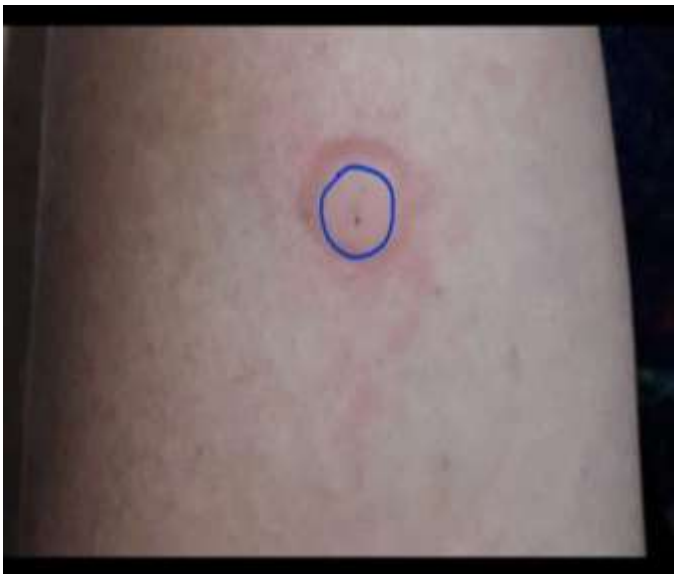

Figure 2. Positive intradermal test result with ketamine (1mg/ml)

Based on the clinical history, examination and investigations, we formed a diagnosis of ketamine induced hypersensitivity.

Discussion

Ketamine, a phencyclidine derivative, is a commonly used agent in both children and adults for sedation, analgesia and intravenous induction. Despite frequent use, the hypersensitivity reactions to ketamine appear to be extremely rare. A meta-analysis by Bellolio et al. revealed no cases of anaphylaxis in 13,883 pediatric sedations, most of whom received ketamine [2]. Common side effects of ketamine include over-sedation, tachycardia, increased secretions, vomiting, laryngospasm, confusion and hallucinations. Bradycardia and hypotension are very infrequent side effects. There are few case reports on allergy and anaphylaxis but most of them involved co-administration of other agents. Bylund et al have described anaphylaxis by intramuscular ketamine as monotherapy [3]. In another case report, an allergic reaction with intravenous ketamine infusion for procedural sedation in the emergency department has been documented [4]. Several factors make the assessment of allergic response in an anesthetic-related reaction difficult. These include the fact that induction drugs are generally administered in quick succession rendering it difficult to identify the actual culprit for hypersensitivity and the clinical manifestations like tachycardia or hypotension can get altered by these concomitantly administered drugs. Draping may prevent the early detection of signs like urticaria or angioedema. It should be noted that history of atopic disease constitutes a risk factor for development of drug allergy and thus, shall be carefully inquired in the pre-anesthetic evaluation. Guyer et al. showed that 55% of patients reported drug allergy history, 48% of them had history of allergic rhinitis, 32% were diagnosed asthmatic, 15% reported a positive history of a severe allergic reaction [5].

We are presenting a case of hypersensitivity to ketamine in a female patient with no previous history of allergy or atopy. As no other drug was administered to the patient before ketamine, the suspicion of ketamine allergy was high. Owing to the low dose of drug given and tourniquet inflation leading to venous stasis in our case, severe systemic response was prevented. Hence, we did not confront life-threatening respiratory or cardiovascular compromise in our case. The transient isolated bradycardia (without other cardiovascular abnormalities) that was witnessed resolved spontaneously. Sheth et al have postulated that oldage, lower baseline vitals, and non-trauma patients are more likely to predict the occurrence of bradycardia after ketamine injection [6]. We believe that the old age and low baseline heart rate could have resulted into the bradycardia response. Benzethonium chloride was the preservative in our ketamine supply. The hypersensitivity test with benzethonium chloride came out to be negative. None of the other patients who were given ketamine from the same vial had any allergic response. There can be development of morbilliform petechial eruption due to tourniquet inflation in thrombocytopenic patients [7]. However, the blanching character of the rash and normal platelet count ruled out that suspicion. The differential diagnosis in our case may include an allergic reaction to latex or ketamine. Latex allergy was ruled out by the history of uneventful previous surgeries where latex gloves were used. Ketamine hypersensitivity was later confirmed by a positive intradermal test. Tryptase level assessment was not available in our institute. The skin testing can be conducted at least four to six weeks after the occurrence of a suspected perioperative allergic reaction, thus allowing for the clearance of suspected drugs and anti-allergic medications [8]. We had attained positive results for ketamine sensitivity in both the tests done on second day and six weeks post operatively. The symptoms in our patient and their improvement with anti-histaminics and steroids were consistent with activation of mast cells and release of mediators like histamine. The Naranjo Adverse Drug Reaction Probability Score was ten indicating a definite ketamine related adverse drug reaction. (Table 1)

QUESTION	YES	NO	DO NOT KNOW
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0

5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9.Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Table 1. Naranjo Adverse Drug Reaction Probability Scale

Interpretation

Total score in our case - 10 (DEFINITE)

0- Doubtful

1-4 - Possible

5-8- Probabe

>9 – Definite

Few studies indicate that ketamine induced allergy is mediated by histamine release and the evidence indicated against an IgE mediated response. However, whether this was the sole mechanism cannot be declared with certainty as there was not complete resolution of rash despite before said treatment. As ketamine does not have a reversal agent, once administered, the physician must be ready to handle the consequences. The only feature of anaphylaxis may be characterized by airway obstruction or cardiovascular collapse in the perioperative period. After an adverse drug reaction, the agent should be discontinued at the earliest. Adequate oxygenation with 100% oxygen, antihistaminic agents (diphenhydramine, pheniramine), corticosteroids (dexamethasone, hydrocortisone), bronchodilators and epinephrine may be administered to control the allergic response. It is essential to avoid the allergen for all future purposes. To the best of our knowledge, there is no published literature documenting incidence of bradycardia with intravenous ketamine hypersensitivity.

Conclusion

Our report aims to send a reminder to all the medical professionals to be highly vigilant and prepared for the rare potentially fatal allergic responses to commonly used drugs. Isolated bradycardia (in absence of other cardiorespiratory abnormalities) and hypersensitivity with intravenous ketamine is a very rare occurrence. All necessary supportive measures like hemodynamic support and advanced airway procedures shall be readily available to efficiently tackle such situations.

Learning points/take home messages

- Incidence of anaphylactic reactions during anesthesia is 1 in 4000 to 1 in 25,000.
- Ketamine is used for procedural sedation and analgesia.
- Hypersensitivity reactions with ketamine are rare.
- With no reversal agent, once ketamine is administered, be ready to handle the consequences.

Conflict of interest

No potential conflict of interest relevant to this article was reported

Funding

Not applicable

Acknowledgments

None

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