

CORRESPONDENCE

Ketamine-induced anaphylactic shock during elective parotidectomy*A case report*

Quentin Mathais, Nicolas Paleiron, Loraine Vatin, Julien Bordes and Pierre E. Gaillard

From the Department of Anaesthesiology and Intensive Care (QM, JB, PEG), Department of Pulmonology (NP), Department of Otorhinolaryngology, Military Hospital Sainte Anne, Toulon (LV) and French Military Health Service Academy Unit, Ecole du Val-de-Grâce, Paris, France (JB)

Correspondence to Dr Quentin Mathais, BCRM Toulon, HIA Sainte Anne – Service de Réanimation-Brûlés 2, Boulevard Sainte Anne, BP 600, 83800 Toulon Cedex 09, France
Tel: +33 483 162 205; fax: +33 483 162 723;
e-mail: quentin.mathais@orange.fr

Editor,

Ketamine is an intravenous hypnotic that is widely used in anaesthesia for its bronchodilating and antihyperalgesic properties and lack of haemodynamic depression.¹ Some adverse effects have been described such as confusion and hallucinations, but anaphylaxis is extremely rare.² We report a patient who presented with anaphylactic shock due to a ketamine infusion during elective surgery. The patient gave written permission to publish this case.

A 70-year-old man with a history of hypertension treated with irbesartan, hydrochlorothiazide and aspirin, dyslipidaemia treated with pravastatine, stage I chronic obstructive pulmonary disease and sleep apnoea syndrome was scheduled for left parotidectomy because of the presence of multiple cysts. He had a general anaesthetic 50 years ago for urgent appendectomy without complication. He did not report any allergies. Pre-operative blood pressure (BP) was 156/92 mmHg and heart rate (HR) was 66 min⁻¹. Physical examination prior to surgery found little to note. General anaesthesia was induced at 13:50 using lidocaine 80 mg, sufentanil 25 µg, propofol 250 mg and ketamine 15 mg. No neuromuscular blocking agents were used. Intubation was easy and anaesthesia was maintained with desflurane and sufentanil. Pre-operative antisepsis was performed with povidone-iodine and we used latex-free surgical gloves. At 14:30, 2 g of intravenous amoxicillin and clavulanic acid were injected at the surgeon's request. At 14:40, the patient developed sudden bronchospasm with increased peak and plateau pressures (60 and 40 mmHg, respectively) requiring a

deepening of sedation. He also exhibited cardiovascular instability with tachycardia up to 120 bpm and arterial hypotension (40/20 mmHg). End tidal carbon dioxide concentration fell from 36 to 20 mmHg. A morbilliform erythematous rash involving the entire body rapidly appeared, evoking the diagnosis of a grade IV anaphylaxis according to the World Allergy Organization Systemic Allergic Reaction Grading System. Intravenous epinephrine titration (0.6 mg), followed by a continuous infusion (1 µg kg⁻¹ min⁻¹), was necessary to restore haemodynamic stability, increasing the BP to 100/50 mmHg and reducing the HR to 80 bpm. Intravenous corticosteroids were given with simultaneous fluid resuscitation. Surgery was aborted, and the patient was admitted to the ICU. The epinephrine infusion was stopped shortly after, and the patient was awakened and discharged on day 2 without any complications. Arterial blood gas analysis showed a lactic acidosis (pH 7.25, lactataemia 4.9 mmol l⁻¹). Histamine and tryptase concentrations 30 min after the event were very elevated, 55 ng l⁻¹ and 48 µg l⁻¹, respectively, and decreased 2 h later (11 ng l⁻¹ and 28 µg l⁻¹), suggesting an IgE-dependent anaphylaxis. Serum-specific IgE testing was negative for amoxicillin and clavulanic acid (<0.1 and <0.35 kU l⁻¹, respectively). Allergy tests were performed 6 weeks later. Skin prick tests and intradermal tests were negative for propofol (10 mg ml⁻¹), xylocaine (10 mg ml⁻¹), sufentanil (50 µg ml⁻¹), amoxicillin/clavulanic acid (10 mg ml⁻¹) and latex. However, they were strongly positive for ketamine (1 mg ml⁻¹), with a 11 mm wheal diameter during skin prick test and a 13 mm wheal diameter (for an initial 6 mm wheal) during intradermal test. Low concentration ketamine intradermal skin testing (0.1 mg ml⁻¹) was also positive with a 12 mm wheal diameter. Provocation testing for amoxicillin and clavulanic acid was negative.

Anaphylaxis during anaesthesia is an unpredictable, dose independent, life threatening and potentially misleading situation.³ Its incidence ranges from 1 in 4000 to 25 000 anaesthetics, and its mortality is estimated to be between 3 and 6%.^{2,3} The two primary triggers of anaphylaxis during anaesthesia are neuromuscular blocking agents and latex; however, all products can be suspected, such as antibiotics, colloids and all other intravenous drugs.³ Two reactions must be distinguished: first, true anaphylaxis, which is a type I, IgE-mediated hypersensitivity reaction; and second, anaphylactoid reaction, not mediated by an IgE or antigen-antibody process.² Clinical symptoms are often similar; however, a specific diagnosis

is important for future anaesthesia. Recognition of anaphylaxis during anaesthesia can be difficult: patients are draped and cannot talk, so cutaneous symptoms such as pruritus or erythema may be missed. In addition, concomitantly administered drugs can alter clinical manifestations, including tachycardia or arterial hypotension, for example. Recognition and adequate diagnosis is nevertheless essential, since re-exposure to the same agent might be fatal. Comorbidities and concurrent medication may affect the severity of anaphylaxis, and the patient's response to treatment. In our case, for example, irbesartan, an angiotensin II receptor blocker, may have interfered with the patient's endogenous compensatory response, leading to a more severe reaction.⁴

Ketamine is a phencyclidine derivative that acts as a noncompetitive antagonist of the *N*-methyl-D-aspartic acid receptor.¹ It is used in emergency medicine for procedural sedation, in anaesthesia, in ICU and even on the ward for analgesia during painful procedures or for palliative care, both in children and adults.¹ Common adverse effects are confusion and hallucinations. Although these are troublesome, they are rarely life threatening. Allergic reactions to ketamine are extremely rare and severe anaphylaxis even more so. Anaphylactoid reactions can be observed occasionally, because ketamine induces the release of histamine from lung and skin mast cells.⁵ However, only a few cases of IgE-dependent anaphylactic reactions have been described, and this is to our knowledge the most severe reported to date.^{6–8}

The initial clinical presentation was misleading: symptoms appeared only 40 min after the start of the ketamine infusion, and amoxicillin and clavulanic acid had been injected 10 min earlier. During the initial resuscitation phase, the anaesthesiologist in charge was confident that the antibiotic injection was responsible for the shock. Acute management of anaphylaxis has been clearly defined, but the most important part is the avoidance of a new exposure to the allergen. In this case, another ketamine infusion (for sedation purposes for example) could be lethal. Practitioners must keep in mind that any drug can induce near fatal allergic reactions, and that any re-introduction before allergy tests must be avoided or, in case of absolute necessity, used with the utmost caution.

For the final diagnosis a combination of mediator measurements and allergic testing are needed to discriminate a posteriori allergic reaction from a nonallergic one and to identify the allergen. Histamine and tryptase blood concentrations are routinely measured in the hospital laboratory. A recent study showed that in severe anaphylaxis (with shock or cardiac arrest),

thresholds of 6.25 ng l⁻¹ and 7.35 µg ml⁻¹, respectively, allowed a diagnosis of immediate allergic hypersensitivity.⁹ Allergic testing includes skin tests and allergen-specific IgE measurement. Ketamine-specific IgE measurement tests are not currently available.¹⁰ However, the association of increased tryptase and histamine levels, and positive skin tests at two different concentrations is likely to be significant and highly suggestive of an IgE-mediated reaction. Current guidelines report the maximal nonirritating concentration of ketamine for a skin prick test to be 10 mg ml⁻¹, and for intradermal testing to be 1 mg ml⁻¹.¹¹

In conclusion, to our knowledge, this is the first report of a peri-operative anaphylactic shock due to intravenous ketamine. Elevated tryptase and histamine levels confirmed mast cell degranulation, and skin prick testing along with intradermal tests confirmed sensitisation to ketamine. This highlights the importance of allergy tests after an anaphylactic episode to find the allergen, and reminds us that any drug can be occasionally responsible.

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References

- 1 Kurdi S, Theerth K, Deva R. Ketamine: current applications in anesthesia, pain and critical care. *Anesth Essays Res* 2014; **8**:283–290.
- 2 Mertes P, Demoly P, Malinovsky J. Hypersensitivity reactions in the anesthesia setting/allergic reactions to anesthetics. *Curr Opin Allergy Clin Immunol* 2012; **12**:361–368.
- 3 Mertes PM, Alla F, Tréchet P, et al., Groupe d'Etude des Réactions Anaphylactoides Peranesthésiques. Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 2011; **128**:366–373.
- 4 Simons FE. Anaphylaxis, killer allergy: long-term management in the community. *J Allergy Clin Immunol* 2006; **117**:367–377.
- 5 Stellato C, Casolaro V, Ciccirelli A, et al. General anaesthetics induce only histamine release selectively from human mast cells. *Br J Anaesth* 1991; **67**:751–758.
- 6 Boynes SG, Lemak AL, Skradski DM, et al. An allergic reaction following intramuscular administration of ketamine and midazolam. *J Clin Pediatr Dent* 2006; **31**:77–79.
- 7 Nguyen T, Baker B, Ferguson J. Allergic reaction to ketamine as monotherapy for procedural sedation. *J Emerg Med* 2017; **24**:562–564.
- 8 Karayan J, Lacoste L, Breuil K. Allergy to ketamine. *Ann Fr Anesth Reanim* 1990; **9**:396–397.
- 9 Laroche D, Gomis P, Gallimidi E, et al. Diagnostic value of histamine and tryptase concentrations in severe anaphylaxis with shock or cardiac arrest during anesthesia. *Anesthesiology* 2014; **121**:272–279.
- 10 Ozcan J, Nicholls K, Jones J. Immunoglobulin E-mediated hypersensitivity action to ketamine. *Pain Pract* 2016; **16**:94–98.
- 11 Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; **68**:702–712.

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