

Hypersensitivity reaction to midazolam: a case of cardio-respiratory failure

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Adv Dermatol Allergol 2020; XXXVII (6): 1012–1013

DOI: <https://doi.org/10.5114/ada.2020.102128>

Midazolam is a short-acting benzodiazepine with a central nervous system depressing action. It is commonly used for conscious sedation for a variety of procedures and for its metabolites pharmacologic properties (sedative, anxiolytic, amnesic and hypnotic activities) [1].

Although allergic reactions to anaesthetics may occur (with an estimated incidence of 1.3500 to 1 : 20000), midazolam is considered to be an exception [2–5]. In fact the most common causes of perioperative allergic reactions include neuromuscular blockers, antibiotics and latex [6, 7].

Therefore, midazolam is often considered a safe drug because it does not have any active metabolites; however, manufacturers have described severe adverse reactions, including respiratory depression or arrest and anaphylactoid or anaphylactic reactions [8–12].

We report herein a rare case of perioperative cardio-respiratory failure probably secondary to midazolam, demonstrated by skin prick tests (SPTs).

Our patient, male, 54 years old, apparently in good health and with normal routine preoperative laboratory tests, chest radiography and electrocardiography, was admitted to the Surgical Unit to undergo elective video-laparoscopic cholecystectomy. He did not have family or personal history of allergic diseases.

In pre-anesthesia, the premedication consisted by intravenous midazolam 2 mg and, after transfer in operating room, propofol 150 mg, fentanyl 50 µg were injected intravenously, monitoring heart activity (ECG), blood pressure, arterial oxygen saturation (SaO₂) and end-tidal CO₂ (ETCO₂). Tracheal intubation was performed after muscle relaxation with atracurium 35 mg intravenously. After a few minutes from the start of surgical procedure, the patient showed bradycardia (35 beats per minute) with wide QRS and ST-segment elevation on the ECG, while blood pressure remained constant. Despite the supplying of oxygen with assisted ventilation and the ad-

ministration of atropine, the patient presented a progressive decrease in the heart rate and blood pressure until asystole that requested the administration of epinephrine 2 mg. Moreover, external cardiac massage was performed for 20 min, when ventricular fibrillation appeared on the ECG monitor. The resuscitation staff proceeded to cardioversion with 200 J biphasic for three times without success; at the fourth attempt they obtained a heart frequency of 190 beats per minute and the onset of peripheral pulses. Subsequently blood pressure and heart frequency came back normal. Moreover, dopamine and plasma expander were administered to our patient. A few hours later tracheal intubation was removed and the patient was fully awake. During the reaction, the tryptase assay was not performed.

After 10 years from this experience in anticipation of a new surgery, the patient was admitted to our Allergy Department of Fondazione Policlinico Universitario A. Gemelli IRCCS.

Allergological evaluation, including allergic clinical history, was carried out with latex, chlorhexidine and the drugs involved in the event. Moreover specific IgE tests for latex, chlorhexidine, morphine and pholcodine (these last drugs a quaternary ammonium homologous to atracurium) were performed.

From the anamnesis, no previous exposure to midazolam or other benzodiazepines emerged.

SPTs with latex and chlorhexidine were negative and the same results emerged after SPT and intradermal test (IDT) with propofol, fentanyl and atracurium at the concentrations described by Brockow *et al.* [13]. The specific IgE tests were all negative. Regarding the midazolam, SPT and IDT were performed respectively until 5 mg/ml and 0.5 mg/ml according to the previous guidelines. The same tests were also performed in five healthy volunteers in order to exclude false positive results. The intradermal test with midazolam 0.5 mg/ml revealed a 6 mm

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Received: 4.03.2019, **accepted:** 7.07.2019.

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diameter wheal and 15 mm diameter erythema, while the SPT at the maximum non-irritant concentration (5 mg/ml) was negative.

So we performed the diagnosis of the cardio-respiratory failure in a patient with IgE mediated allergy to midazolam. The diagnosis is supported by negative allergological tests in healthy controls. Finally, we advised the patient to avoid the use of midazolam in the next surgery in general anaesthesia.

In this report we showed the case of a cardio-respiratory failure following the induction of anaesthesia in a patient with positive allergological evaluation to midazolam.

In literature we found more reports about midazolam hypersensitivity.

The first case reported a severe facial oedema and itching in a parturient woman [14]. In the second one midazolam caused angioedema and bronchoconstriction [15], while in another one the patient presented hypotension that required the administration of ephedrine [16].

Moreover, there are also two case reports that described allergic reactions after intranasal administration of midazolam [17, 18]. Ates *et al.* [19] described a case of an acute coronary syndrome after an intravenous injection of midazolam with a serum tryptase increase during a transurethral prostatectomy, but no serologic or cutaneous allergy testing was performed to define the immunological features of the anaphylactic reaction.

To our knowledge, only in 2 cases of an adverse reaction to intravenous midazolam, the allergological evaluation showed a positive reaction. Hwang *et al.* [12] performed only a skin prick and intradermal test with positive results, while Bernardini *et al.* [8] showed a positive intradermal test and IgE immunoassays for midazolam with a radioactive uptake of 0.66% and a non-specific binding of 0.41%.

In our case, the main symptom was a cardiovascular failure characterized by initial bradycardia and wide QRS and ST-segment elevation on the ECG that simulated a myocardial infarction. We suppose that in this case, midazolam caused the release of histamine from mast cells, which triggered vasospasm of coronary arteries that caused the cardiac arrest.

In conclusion, midazolam hypersensitivity is relatively rare, so it is difficult to research the potential risk factors. However, although this drug is generally regarded as safe and well tolerated, in some patients it could rarely induce serious life-threatening allergic reactions. In these cases, an emergency treatment and a serum tryptase assay are always recommended to evaluate the causative symptoms in the suspicion of an anaphylactic reaction.

Acknowledgments

All the authors contributed equally to this work.

Conflict of interest

The authors declare no conflict of interest.

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