

# Hypersensitivity Reaction to Midazolam

## Abstract

The incidence of hypersensitivity due to anesthesia in children is 1/7741. Hypersensitivity reactions are a result of either an immunologic mechanism (allergic or anaphylactic reaction) generally mediated by immunoglobulines E (IgE) or immunoglobulines G (IgG) antibodies or a non immunologic mechanism (pseudo-allergic or anaphylactoid reaction) related to different phenomenon such as non specific histamine liberation. In children, latex is the principal cause of anaphylaxis during anesthesia (41%) followed by non depolarizing muscle relaxants (19%) and antibiotics (9%); anaphylaxis due to hypnotics is rare (2,43%) and midazolam is responsible in only 0,5% of the cases. Anaphylaxis during anesthesia is mediated by immunoglobulines E antibodies in 42% of the cases in children. We describe here a case of a six year old child who presented a hypersensitivity skin reaction to midazolam thirty minutes after intrarectal midazolam administration. It was a generalized rash of the whole body without pruritis. The prick tests realized six weeks after the reaction were negative and the intradermoreaction was positive to midazolam confirming the hypersensitivity reaction to midazolam. A hypersensitivity identification card to midazolam was delivered to the patient.

**Keywords:** pediatric anesthesia; anaphylaxis, allergy, hypersensitivity, midazolam

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**Abbreviations:** IgE, immunoglobulines E; IgG, immunoglobulines G; MRI, magnetic resonance imaging

## Introduction

The annual incidence of generalized allergic reactions is higher in children (9.3/1000 admissions) than in adults (2.6/1000 admissions). Anaphylaxis is the most serious allergic reaction characterized by generalized signs and symptoms that can compromise the vital prognosis and can lead to death in 2% of the cases.<sup>1</sup> The incidence of anaphylactic reactions in France has been evaluated to 1 over 13000 general and loco regional anesthetics.<sup>2</sup> The incidence of allergy during anesthesia in children is 1 over 7741 anesthesia.<sup>3</sup> Three risk groups of anaphylaxis during anesthesia have been identified: patients who have presented clinical signs of immediate hypersensitivity reaction in the perioperative period and who did not have a diagnostic investigation; patients who presented clinical signs of allergy immediately after exposure to latex or to fruits or vegetables which have cross reactions with latex such as avocado, kiwi, banana, chestnut, papaya, pineapple...; patients who have been operated several times. An allergologic investigation is recommended in all these patients.<sup>3</sup> In children latex is the first cause of anaphylaxis (41%) during anesthesia, followed by non depolarizing muscle relaxants (19%) and antibiotics (9%); anaphylaxis due to hypnotics is rare (2.43%) and midazolam is responsible in only 0.5% of the cases. In children and in adults anaphylaxis during anesthesia is mediated by IgE in 42 % and 72 % of the cases respectively.<sup>4</sup> In adults non depolarizing muscle relaxants are the first cause (58%) of anaphylaxis during anesthesia followed by latex (19%) and antibiotics (12%). The female gender is more concerned, this can be explained by the hormonal role as this is not observed before teenage.<sup>4,5</sup> Anaphylaxis occurs during general anesthesia in 91 % and during local regional anesthesia in 9% of the cases.<sup>5</sup> There are different grades of clinical severity in anaphylactic and anaphylactoid reactions varying from generalized skin reactions to multiorgane failure, cardiac arrest and or death.

## Case report

We reported here a case of a six year old girl admitted for a cervical magnetic resonance imaging (MRI) under general anesthesia for cervical adenopathies discovered by ultrasound imaging. The personal history was characterized by a subdural hematoma diagnosed four months before after an accidental fall without any other signs and symptoms. There was no history of allergy and she didn't take any medication. She received in the hospitalization ward 5mg of intrarectal midazolam. On admission in the induction room 30minutes after premedication with midazolam, physical examination revealed a maculo-erythematous skin reaction without pruritis of the face, truncus and the limbs. The mother precised that the rash appeared ten minutes after midazolam was administered. The patient's heart rate, oxygen saturation, respiratory rate, blood pressure and body temperature were normal. Cardiopulmonary auscultation was also normal. The skin eruption disappeared after 1mg/kg intravenous methylprednisolone was administered. Induction of anesthesia was realized with sevoflurane via facial mask and a bolus of propofol. Maintenance of anesthesia was done with sevoflurane and endotracheal intubation. No adverse incident was observed during anesthesia and the vital signs were in the normal range. Plasmatic tryptase was normal at 4.3 microgrammes/liter ( $\mu\text{g/l}$ ) (normal range  $<11.4\mu\text{g/l}$ ). Plasmatic IgE specific to latex were also negative ( $<0.1\text{kU/l}$  (kilounits/liter)). The IgE specific to food allergens ('trophatop enfant') were also negative. Skin tests were realized six weeks after the skin reaction. Prick tests with midazolam and latex were negative. Intradermoreaction with midazolam was positive. Vital signs were normal during the skin tests. An identity card for midazolam allergy was delivered to the patient.

## Comment

Perioperatively the anesthesiologist mostly deals with immediate hypersensitivity reactions. These reactions are due to an immunologic mechanism (allergic ou anaphylactic reaction) normally mediated by IgE or IgG antibodies, or non immunologic mechanism (pseudo-allergic

or anaphylactoid reaction) in relation with different pathophysiologic mechanisms such as nonspecific histamine liberation, kinine-kallicrein system and complement activation leading to an excessive production of bradykinine and activation of leucotrienes synthesis.<sup>6-9</sup> When a hypersensitivity reaction occurs during anesthesia regardless of the severity, it is recommended to measure serum tryptase and histamine as soon as possible, plasmatic IgE specific to non depolarizing muscle relaxants and latex and to realize an allergologic investigation 4 to 6 weeks to 2 years after the reaction.<sup>9-11</sup> The investigation includes skin tests (prick tests, intradermoreaction), measurement of serum specific immunoglobulines E (IgE) or white blood cells activation or reintroduction test according to the situation. Preventing allergic risk begins in the perioperative period from the surgical indication to the anesthesia consultation.<sup>12</sup> Primary prevention consists in not exposing patients to substances that can induce an immediate hypersensitivity reaction in the perioperative period (free latex operation rooms, avoiding general anesthesia, preferring loco regional anesthesia and preferring induction with sevoflurane induction in children since no allergy to halogens has been reported). Secondary prevention implicates not re exposing the patient to an allergen to which he is sensitized. In this case report several remarks can be emphasized: Histamine wasn't analyzed for technical reasons related to the sample. Histamine analysis could have precised whether the reaction implicated histamine liberation or not. Because of the short plasmatic histamine half-life which is often to twenty minutes<sup>13</sup> the results could not be relevant because the blood sample was taken thirty minutes after the reaction. It is recommended to dose plasmatic histamine very early (within fifteen minutes after the reaction). In order to have relevant results. In case of a minor reaction such as isolated skin reactions, tryptase can be negative which the case here was.<sup>13</sup> Tryptase must be dosed between fifteen minutes and two hours.<sup>14</sup> Plasmatic immunoglobulines E (IgE) against midazolam were not measured also for technical reasons related to the blood sample. These specific IgE which are not dosed for all allergen scan be detected some time after the reaction (four weeks to two years after) and their presence in the plasma can confirm an immunoglobuline E mediated reaction. In our case we cannot tell if the reaction was mediated or not by IgE. The positive intradermoreaction confirmed the diagnosis of an immediate hypersensitivity reaction and an identity allergic card to midazolam was delivered to the patient. Midazolam is widely used in pediatric anesthesia for premedication, fortunately hypersensitivity reaction to this substance remains rare (0,5%). The importance of premedication in pediatrics by pharmacological or non-pharmacological means has been established.<sup>15</sup> Other pharmacologic substances like clonidine can be good premedication alternatives in children in case of a contraindication to midazolam.<sup>16,17</sup>

## Conclusion

The diagnosis of hypersensitivity allergic or non-allergic reactions in anesthesia leans on different elements including allergologic and laboratory tests as well as the clinical anesthetic report. We emphasize here the importance of allergy testing investigation in patients who present a suspected reaction to a substance regardless of the severity of the symptoms and signs in order to prevent are exposure to the same substance which can lead to a more serious adverse reaction.

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## Conflicts of interest

The authors declare that there are no conflicts of interest.

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