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Perioperative midazolam hypersensitivity in a seven-year old boy

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To the editor,

Midazolam is a short-acting benzodiazepine with a central nervous system depressing action. The pharmacologic properties of midazolam and its metabolites (similar to those of other benzodiazepines), include sedative, anxiolytic, amnesic and hypnotic activities. The favorable clinical aspects of the use of benzodiazepines are the result of a reversible allosteric interaction with the (gamma)-amino butyric acid (GABA) receptor A, that accounts for the major inhibitory neurotransmitter pathway within the central nervous system (1). Midazolam is rapidly absorbed after oral administration: the absolute bioavailability of syrup in pediatric patients is about 36%, and reaches 90% with the intramuscular route.

We report herein a rare case of perioperative midazolam hypersensitivity in a boy admitted for a surgical procedure. The patient, male, aged 7 years, was admitted to our Unit for an elective adenoidectomy. He had a family history of allergic diseases (father asthmatic). He was suffering from allergic asthma and rhinitis (sensitized to grass pollen and mite). In the preanesthetic room, after oral intake of 0,5 mg/kg of midazolam (no other pre-anesthetic drug was used) he immediately developed dyspnea with wheezing, prolonged expiration, signs of respiratory distress and failure, with a peripheral blood saturation <90%. Nasal flaring, orthopnea, accessory muscle use were also documented, without cutaneous signs. Arterial pulse oxygen saturation and noninvasive blood pressure were monitored. Blood pressure was normal (97/59 mm/Hg) but his oxygen saturation decreased gradually to 90%. High-flow supplementation oxygen was given (5 L/minute) by facemask and he received also oral corticosteroids (betamethasone 4 mg), nebulized short-acting beta agonists, (salbutamol 6 puff) and intravenous fluids. Symptoms subsided within 1 hour. Serum tryptase dosage was not performed.

After two months, an allergy investigation was carried out. No previous exposure to midazolam or other benzodiazepines emerged from the clinical history. IgE immunoassays for midazolam with epoxy-activated sepharose as solid phase was: radioactive uptake 1.93%, non-specific binding 0.70%. Skin prick test for Midazolam (5 mg/ml) was negative, while intradermal test (0.5 mg/ml) revealed a clearly positive reaction (wheal diameter was increased of 5 mm and erythema diameter of 10 mm from baseline) according to Brockow and coworkers

(2). SPT to latex with a commercial extract (ALK-Abellò) was negative. One year after the event, the allergy investigation was repeated. IgE immunoassays for midazolam was: radioactive uptake 0.66%, non-specific binding 0.41%. At intradermal test the wheal diameter was increased by 3 mm and the erythema diameter by 7 mm from baseline.

Several drugs are commonly used by anesthesiologists during the perioperative period. Many of these drugs can display side effects that are usually dose-related, sometimes leading to severe immune-mediated adverse reactions. Anaphylaxis is the most severe immune-mediated reaction, generally occurring on re-exposure to a specific antigen. The release of proinflammatory mediators is also involved. Anaphylactic-like reactions may occur through a non-immunoglobulin E-mediated release of mediators from mast cells or via the complement system activation. Muscle relaxants and latex account for most cases of anaphylaxis during the perioperative period. Usually, symptoms include: bronchospasm, generalized urticaria and cardiovascular collapse (3). The incidence of anaphylaxis and anaphylaxis-like reactions during anesthesia is very difficult to estimate but it has been estimated to range from 1 in 3,500 to 1 in 13,000 cases (4). Allergic reactions to benzodiazepines are extremely rare. The Cremophor EL solvent was reported to be responsible for most reactions to benzodiazepines. Diazepam is more likely than midazolam to cause anaphylactic reactions, because of the propylene glycol solvent that replaced Cremophor EL. The active metabolite desmethyldiazepam may be responsible for the cross-reactivity with other benzodiazepines. Midazolam is generally considered a safe drug, because it does not produce active metabolites (5). Although anaphylactoid reactions to midazolam have been occasionally reported, no serologic or cutaneous testing was performed or described (6-7). Only in one case of adult patient intradermal test revealed a positive reaction to midazolam (8). To our knowledge, this is first report of midazolam hypersensitivity in a child during the perioperative period. In the case herein reported, the retrospective diagnosis was based on serologic and skin specific tests. One year after the episode, specific IgE were decreased but skin test remained positive, suggesting that this diagnostic approach is probably more sensitive for immediate reactions (Type I) to this drug. Of note, and as expected, the patient did not show previous sensitization symptoms to midazolam.

It is well known that many drugs belonging to a certain drug class, may differ in immune reactivity only for the characteristics of the in side chains. Thus the reactivity of the immune system to one compound of one drug class may result in unexpected cross-reactivity to similar compounds. This cross-reactivity of the immune system with similar drugs depends on the structural affinity and precursor frequency of drug-specific T (or B) cells. Drugs, which may differ in only an OH group, might be result more cross-reactive than drugs which are different in a longer side-chain (9). Cross-reactivity in IgE-mediated reactions is more problematic, since in sensitized individuals, small amounts of drugs (which normally behave as haptens) may induced a cross-link drug-specific IgE on mast cells by hapten-carrier complexes. Therefore, acute symptoms reflecting cross-reactivity may arise even if the amount of drug is very low and the level of cross-reactivity is limited and restricted to a small part of drug-specific IgE. Other studies would be needed about possible cross-reactivity of midazolam with other drugs or other substances occurring in nature (10).

This case also confirms that skin reactivity persists for a longer period than circulating IgE, and is therefore more sensitive. In conclusion this case demonstrates that midazolam can induce hypersensitivity reactions. Accordingly we advise that this possibility should be considered when midazolam is administered during perioperative period in pediatric patients even if the clinical history is not indicative.

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