A. Charles[1], F. Lavaud[2], A. Gallet[1], C. Boulay-Malinovsky[1], P.M. Mertes[3], J.M. Malinovsky[1]

Anaphylactic reaction to hydroxyzine in an anesthetized patient

[1]Service d'Anesthésie et Réanimation, Pôle URAD, CHU, Hôpital Maison Blanche, 51092 Reims; [2]Service des Maladies Respiratoires et Allergiques, Pôle TCV, CHU, Hôpital Maison Blanche, 51092 Reims; [3]Service d'Anesthésie et Réanimation, CHU, Hôpital Central, 54045 Nancy, France

Key words

hydroxyzine, anaphylaxis, anesthesia, premedication, perioperative allergy

Summary

A case of anaphylaxis occurring during a general anesthesia is presented. The reaction was severe with bronchospasm and hypotension (grade 2 in the severity of per-operative anaphylactic shock). The responsibility of hydroxyzine, administered for premedication was suspected by intradermal testing with the molecule, which was twice positive at a 10^{-2} dilution of the commercial solution. The same test remained negative in 5 control subjects. All the other drugs received during anesthesia gave negative results. Using the same protocol excepted for the use of hydroxyzine a new general anesthesia could be performed under a premedication with dexchlorpheniramine without any allergic reaction. Anaphylactic reactions are very rare with hydroxyzine used in premedication for anesthesia in regard to the large prescription of the drug. Only two previous cases were reported but attention of the allergist must be also pointed towards the medications received in the perioperative period as for the anesthetic drugs

Introduction

Histamine release may induce life-threatening side effects associated with drugs as anesthetics, antibiotics or contrast media. While the mechanism of release during an anesthesia is mainly immunologic, a part of the reactions may be prevented by the use of histamine receptor antagonists (1). Hydroxyzine hydrochloride is a histamine H1 receptor antagonist that is effective in the treatment of chronic urticaria, dermatitis, and histamine-mediated pruritus. As it has also sedative properties, it is a premedication widely used before an anesthesia in allergic patients (1), administered orally or intravenously.

Hypersensitivity reactions to hydroxyzine are sparse, mainly of delayed mechanism with cutaneous signs (2-8). We want to report the case of a patient who presented an anaphylactic reaction related to hydroxyzine during an anesthesia. We described an alternative premedication proposed to the patient for further anesthesia.

Case report

A 60 yr old woman was scheduled for thyroidectomy because of toxic nodules. Her past history revealed an uneventful left thyroidectomy 25 yr ago. In her medical his-

tory it was noted an arterial hypertension, a dyslipidemia, no respiratory problem. She was not atopic, but reported skin rashes or pruritus with paracetamol, aspirin, codeine, some antihistamines and many anti-inflammatory drugs. She took daily losartan, levothyroxine, fenofibrate, and lorazepam at evening.

Just before surgery she received 100 mg of i.v. hydroxyzine plus 80 mg of methylprednisolone. General anesthesia was induced by i.v. propofol, midazolam and sufentanil without the use of curare. A tube was easily inserted in the trachea and anesthesia was maintained by sevoflurane. However, 10 minutes after i.v. injection of anesthetics, she experienced a bronchospasm with an increasing in airway pressures associated with mild hypercarbia at 55 mmHg and a decrease in arterial blood pressure from 130/80 to 90/50 mmHg. The intensity of bronchospasm decreased with terbutaline and budesonide spray plus 40 mg of i.v. methylprednisolone. Surgical procedure started by preparing the skin with alcoolhic povidone. Neverveless, a few minutes after, a new episode of bronchospasm occurred with a drop in pulse oxymetry at 0.90 despite the use of FiO2 1. Surgery was cancelled. The patient received 0.25 mg and continuous infusion of i.v. terbutaline. She was admitted in the post-anesthetic care unit (PACU). Thirty minutes after the onset of the bronchospasm, blood was sampled to determine the concentrations of histamine and tryptase. As respiratory function remained stable, tracheal tube was removed 20 minutes later. Terbutaline administration was stopped in the evening. In operative room and PACU no cutaneous signs were observed. Three months later, the patient was addressed to our allergy clinic to diagnose the reaction and propose an alternative premedication for further anesthesia.

The allergologic check-up was assessed with blood chemistries, cutaneous tests and provocative reintroduction test.

At time of the anaphylactic reaction, tryptase level was at 80 mcg.L^{-1} (N < 13 mcg.L^{-1}), and histamine at 150 nM.L^{-1} (N <10 nM.L^{-1}).

At time of the allergologic assessment, the pulmonary function was normal and the provocative test to metacholine was negative with a Pd 20 > 2000 mcg. Basal level of tryptase was 3 mcg.L^{-1}, and histamine 11 nM.L^{-1} discarding any pathology as mastocytosis. Total IgE level was considered as normal at 36 U.mL^{-1} (N <100) and specific IgE against latex were negative in CapRAST^{R}.

Skin tests were performed in accordance with drug allergy European Network of Drug Allergy/European Academy of Allergology and Clinical Immunology recommendations (9) .The cutaneous reactivity was important to codeine and histamine controls, and negative for saline solution. The cutaneous prick and intradermal testing showed negative responses for latex, midazolam, propofol and sufentanil. The skin prick-tests (SPTs) were also negative to hydroxyzine (dilution10^{-1} of the commercial solution), methylprednisolone, and povidone (under several galenic forms). Intradermal tests (IDTs) were negative excepted for hydroxyzine which induced a wheal of 14 mm when an injection of 0.05 ml at 10^{-2} dilution of the commercial solution (100mg in 2 mL) was performed.

In order to propose an alternative premedication for further anesthesia, a new screening by cutaneous tests and provocative reintroduction tests was performed several months later. The skin tests were identical, with a wheal of 15 mm after hydroxyzine (at 10^{-2}), contraindicating a reintroduction challenge test with hydroxyzine. The skin tests (SPTs in native form for all drugs, IDTs from 10^{-3} to 10^{-1} of the commercial solution for disposable soluble forms) with several antihistaminic agents (cetirizine, dexchlorpheniramine, ebastine, loratadine and desloratadine, mequitazine) were negative. So we choose to perform an oral reintroduction test with dexchlorpheniramine. Finally, a total dose of 6.6 mg of dexchlorpheniramine (step by step 4.1 mg orally and 2.5 mg intramuscularly) was given without any immediate or delayed adverse reaction.

Under 2 mg of dexchlorpheniramine and 0.25 mg of alprazolam premedications given orally before thyroidectomy, general anesthesia with propofol, sufentanil and sevoflurane was uneventfully performed. The follow-up of our patient during 3 days was simple without any allergic reaction.

Discussion

There are only few case reports quoted in the Medline database, and hypersensitivity reactions with histamine receptor antagonists are mostly of delayed type (2-8). The signs reported with hydroxyzine are skin rashes, urticaria or photosensibilisation, erythema multiform with positive patch tests, fixed drug eruption or systemic eczema. There are only 2 case reports of hypersensitivity reactions to hydroxyzine during an anesthesia (10,11). In the first case hypoxemia and skin eruption were noticed during an orthopedic procedure (10), and in the second a generalized urticaria occurred 30 minutes after hydroxyzine premedication during cardiac surgery (11). In the former case skin tests were positive to hydroxyzine, in the second case

an immunological mechanism has been evoked because lymphocyte stimulation test turned positive to hydroxyzine. In our patient, a severe bonchospasm associated to an arterial hypotension occurred after induction of anesthesia. The high concentrations of tryptase and histamine after the reaction and the positivity of intradermal tests (positive twice) supported the diagnosis of an immediate hypersensitivity reaction to hydroxyzine.

As positive skin tests with hydroxyzine have not been yet reported, we performed the same tests to 5 control subjects. They remained all negative in IDTs up to a 10^{-1} concentration of the commercial solution. In order to rule out the responsibility of compounds found in hydroxyzine tablets, which are also contained in surgical antiseptic distemper, we tested povidone in SPTs, which were all negative in our patient.

This is the first case of a well documented immediate hypersensitivity reaction to hydroxyzine. Mostly curares, latex and antibiotics are responsible for such events during an anesthesia (12). The anaphylactic reaction to hydroxyzine was annoying because such agent is often given to neutralize the effects of histamine release after administration of anesthetics, and histamine receptor antagonists are the premedication of choice in drug sensitive patients. As our patient must be again anesthetized, it was necessary to find an alternative to hydroxyzine as premedication. Among the histamine receptor antagonists, cetirizine and hydroxyzine share a common core, the piperazine core. We speculated that epitope for hypersensitivity reaction in our patient was perhaps the piperazine core (3,5,6,13) because the patient reported previous rashes with cetirizine. However, SPT remained negative with cetirizine but also with hydroxyzine certainly due to a lower sensitivity of SPT compared to IDTs (9)

Cetirizine was not suitable for IDTs so we could not conclude about a sensitization to the drug without a provocative test which was not performed for ethical reasons.

Nevertheless, to find an alternative to hydroxyzine as premedication before an anesthesia, we decided to perform provocative test with an other compound family rather than with cetirizine in such indication. In regard to its sedative properties and considering a possible iv administration, we test dexchlorpheniramine by using IDTs and oral and systemic reintroduction tests. As skin tests and provocative challenge were negative we proposed it as premedication before the new anesthesia, which was uneventful.

In conclusion, we report a per-operative anaphylaxis to hydroxyzine used in premedication before an anesthesia. The allergological investigation supports the hypothesis that it may be considered as a potential allergen for immediate hypersensitivity reaction. By using screening tests and provocative reintroduction test we found an alternative to hydroxyzine to prepare the patient before the new anesthesia. Moreover, our case report underlines that it is important to test also the molecules used for premedication in the diagnosis of immediate hypersensitivity reactions occurring during an anesthesia.

References

1. Mertes PM, Laxenaire MC, Lienhart A et al. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. J Investig Allergol Clin Immunol 2005;15:91-101.
2. Ash S, Scheman AJ. Systemic contact dermatitis to hydroxyzine. Am J Contact Dermat 1997;8:2-5.
3. Assouere MN, Mazereeuw-Hautier J, Bonafe JL. [Cutaneous drug eruption with two antihistaminic drugs of a same chemical family: cetirizine and hydroxyzine]. Ann Dermatol Venereol 2002;129:1295-8.
4. Tamagawa R, Katoh N, Nin M, Kishimoto S. [A case of drug eruption induced by hydroxyzine pamoate]. Arerugi 2006;55:34-7.
5. Lew BL, Haw CR, Lee MH. Cutaneous drug eruption from cetirizine and hydroxyzine. J Am Acad Dermatol 2004;50:953-6.
6. Chang YS, Kwon HS, Cho SH et al. A case of urticaria induced by both hydroxyzine and cetirizine but not by levocetirizine. Allergy 2007;62:819-21.
7. Cohen HA, Barzilai A, Matalon A et al. Fixed drug eruption of the penis due to hydroxyzine hydrochloride. Ann Pharmacother 1997;31:327-9.
8. Michel M, Dompmartin A, Louvet S et al. Skin reactions to hydroxyzine. Contact Dermatitis 1997;36:147-9.
9. Brockow K, Romano A, Blanca M, Ring I, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002; 57 : 45-51
10. Okuda T, Karasawa F, Satoh T. [A case of drug allergy to hydroxyzine used for premedication]. Masui 2000;49:759-61.
11. Urabe K, Fujii K, Tezuka M et al. [A case of acute urticaria from hydroxyzine hydrochloride used for preanesthetic medication]. Masui 2000;49:890-2.
12. Mertes PM, Laxenaire MC, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. Anesthesiology 2003;99:536-45.
13. Cravo M, Goncalo M, Figueiredo A. Fixed drug eruption to cetirizine with positive lesional patch tests to the three piperazine derivatives. Int J Dermatol 2007;46:760-2.