

Anaphylaxis caused by immediate hypersensitivity to topical chlorhexidine in children



Chlorhexidine is a cationic polybiguanide that has bacteriostatic, bactericidal, and fungicidal activity. It is adsorbed by the proteins that contain phosphate in the bacterial cell wall, causing the breaking of the bacterial cytoplasmic membrane and the leakage of cytoplasmic components.¹

Hypersensitivity reactions to chlorhexidine have been reported since 1971, and although uncommon, these reactions seem to be increasing as the use of chlorhexidine is spreading.² Since the first suspected IgE-mediated reaction was described in 1984,³ similar reports have been published, although anaphylaxis is still uncommon and rarely described in children.⁴

Layton et al¹ proposed that bisbiguanides, like chlorhexidine, are able to haptenate by covalently conjugating with tyrosine, lysine, and tryptophan, probably through nucleophilic groups.¹ Diagnosis of immediate reactions have been based on skin tests and specific IgE (sIgE) determinations.⁵ Other tests, such as the sulfidoleukotriene stimulation test or basophil activation test (BAT), have been also used.⁶ We describe 2 cases of anaphylactic reactions in children attributable to topical chlorhexidine use and in whom hypersensitivity mechanism was demonstrated by tryptase, skin prick test (SPT), sIgE test, and BAT results.

A 3-year-old boy who underwent hypospadias surgery developed sudden hypotension (blood pressure, 40/20 mm Hg) and desaturation (oxygen saturation, 80%). After response to an intravenous epinephrine bolus (0.01 mg/kg) and ephedrine (0.4 mg/kg), cardiorespiratory symptoms, facial swelling, and systemic urticaria reappeared, so surgery was suspended, and the patient required further treatment at a pediatric intensive care unit with dopamine (10 µg/kg per minute), norepinephrine (2 µg/kg per minute) continuous infusions, volume expansions with physiologic solution, intravenous dexchlorpheniramine (0.2 mg/kg every 8 hours), methylprednisolone (4 mg/kg daily) nebulized salbutamol (0.2 mg every 2 hours), and furosemide (0.5 mg/kg). Vasopressor support and medication requirements lowered progressively and ceased in 12 hours.

The patient had received the following during the procedure: intravenous rocuronium and fentanyl (45 minutes before the symptoms onset), epidural levobupivacaine (30 minutes before), and topical 0.5% chlorhexidine digluconate at urethral mucosal (previously used routinely and well tolerated at home) as well as local exposure to latex gloves. Tryptase levels (ThermoFisher Scientific, Uppsala, Sweden) were measured (Table 1).

Cutaneous tests were performed 3 weeks after the episode, according to the European Network for Drug Allergy/European Academy of Allergy and Clinical Immunology guidelines.⁷ Normal saline solution and histamine (10 mg/mL) were used as negative and positive controls, respectively. SPT results were considered positive when the mean wheal diameter reached at least 3 mm per flare greater than 6 mm. The results of SPTs and intradermal tests with fentanyl, rocuronium, cisatracurium, atracurium, and bupivacaine were negative. The SPT result with latex was negative. The SPT result with 2% chlorhexidine digluconate revealed a positive result (10-mm mean wheal and 25-mm flare) (Table 1). The sIgE test result (ImmunoCAP FEIA, Thermo Fisher Scientific) was positive for chlorhexidine (Table 1) and negative for bupivacaine, morphine, and latex. Subcutaneous challenge with bupivacaine (0.6 mL) was well tolerated.

Table 1

In Vivo and In Vitro Test Results

Variable	Case 1	Case 2
Chlorhexidine SPT result, mm (concentration)	12 × 8 (2%)	10 × 8 (0.2%)
Total IgE, U/mL	140	140
sIgE chlorhexidine, kU/L	2.31	24.5
Serum tryptase, µg/L		
During the episode	13	13.3
Baseline	<1	4.5
BAT, % activated basophils		
Basal activation	4.26	6
Positive control (anti-IgE)	45.10	32
Chlorhexidine (0.05 mg/mL)	7.86	58
Chlorhexidine (0.25 mg/mL)	9.34	53

Abbreviations: BAT, basophil activation test; sIgE, specific IgE; SPT, skin prick test.

BATs performed with rocuronium (0.5–0.25 mg/mL), cisatracurium (0.6–0.3 mg/mL), and atracurium (3–0.5 mg/mL)⁸ produced negative results. BATs with chlorhexidine produced positive results (Table 1).

A 12-year-old boy with atopic dermatitis and dust mite–induced bronchial asthma attended the pediatric emergency department after a casual injury with abrasion in the right knee. After topical application of a 1% chlorhexidine digluconate solution, which previously caused local erythema and pruritus, he developed immediate generalized urticaria, with lip and tongue angioedema, cough, and dyspnea (oxygen saturation, 93%). He received intramuscular epinephrine (0.01 mg/kg), intravenous methylprednisolone (2 mg/kg), dexchlorpheniramine (0.3 mg/kg), and nebulized salbutamol (5 mg). He recovered within 45 minutes. Tryptase levels (Thermo Fisher Scientific) were measured (Table 1).

The allergy workup was performed 4 weeks after the episode. The results of SPTs with 0.2% chlorhexidine digluconate, sIgE, and BAT with chlorhexidine were positive (Table 1).

Allergic reactions to chlorhexidine are not common, considering its widespread use. Anaphylaxis caused by chlorhexidine is even rarer in children. However, chlorhexidine can induce life-threatening reactions even after topical use and is now considered one of the main culprits of the IgE-mediated perioperative reactions.⁹

It is thought that topical exposure to damaged epithelium (skin excoriations, abrasions, and lacerations, no matter how big or small they are) or to mucosae (even of small amounts¹) may facilitate the onset of a severe allergic reaction, as occurred in our patients. Its use is not limited to sanitary use, but it can also be found in cosmetics, suppositories, and some antacids. Therefore, thorough information must be given to chlorhexidine allergic patients.

Severe reactions usually occur after previous mild reactions, so some authors have suggested performing a SPT for chlorhexidine in every patient with a reaction after any medical procedure.¹⁰ However, reaction to chlorhexidine can appear without previous known topical or systemic exposure as occurred in case 1.

Allergy to chlorhexidine has been previously defined as a relevant clinical reaction combined with 2 or more positive test results. The combination of SPT and sIgE results have the highest estimated sensitivity and specificity values.⁵ In our patients, these criteria were fulfilled in in vivo (skin tests) and in vitro tests. In both our cases through SPTs, we tested 2% and 0.2% concentrations of the commercial presentation of the product responsible for

anaphylactic reactions without seeing systemic reactions. The validated chlorhexidine nonirritating concentration is 5 mg/mL; therefore, it is highly unlikely that inferior concentrations pose a potential risk for anaphylaxis. In vitro test (IgE determinations and BATs) results were all positive, revealing the usefulness of these tools to obtain an accurate diagnosis, as previously described.^{5,6} The BAT in both patients was performed under 2 different conditions to determine the optimal basophile activation concentration for each sample. There is lack of a dose response in the BATs done in case 2. In our opinion, with the lowest pharmaceutical concentration, you can see basophile activation. On the contrary, with the highest concentration, you can see cytotoxic effects or unspecific basophile activations, causing technical interpretation problems. The elevated serum tryptase level in our patients was indicative of mast cell degranulation during the episode.

True incidence of chlorhexidine allergy is unknown because chlorhexidine is an underestimated antigen of anaphylactic reactions. Although rarely described, it can also appear in children. Increased awareness of the risk of this widely used antiseptic is needed, especially at all emergency departments, perioperative environments, and intensive care units.

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Manifestations of hereditary angioedema



Hereditary angioedema (HAE) is characterized by sudden edema of the larynx, lips, oropharynx, periorbital tissues, abdomen, or limbs.¹ Episodes of severe headaches and visual disturbances are also commonly seen in patients with HAE. Symptoms usually resolve within minutes to hours. Neurologic manifestations of HAE are more rare, but there have been case reports in the literature involving cerebral edema^{2,3} and stroke-like episodes.⁴ Local cerebral edema has been implicated in transient ischemic attacks (TIAs); although the mechanism is not well delineated, rapid onset of edema might temporarily reduce blood flow in certain blood vessels, leading to TIA symptoms, which resolve as the edema resolves.

We report the cases of 3 patients who have been diagnosed with HAE type 1 and who have neurologic manifestations of this disorder (Table 1). Patient 1 is a 27-year-old white woman who was diagnosed with HAE type 1 at 26 years of age. Her symptoms included swelling of the limbs and abdomen, severe fatigue, chronic migraine, dizziness and poor balance, recurrent episodes of cognitive problems, and severe bouts of opsoclonus and myoclonus. The latter resulted in blurry vision and, on some occasions, double vision and involuntary twitches of the muscles of her shoulders, arms, and sometimes legs. These symptoms were having a markedly detrimental effect on the patient's quality of life as she was attending medical school and facing enormous challenges because of the symptoms mentioned above. Brain magnetic resonance imaging (MRI) was performed in November 2010, but the results were essentially normal. On the basis of her clinical presentation and neuroimmune markers, she was initially treated

with intravenous immunoglobulin (IVIG; 380 mg/kg every 2 weeks) for the symptoms of opsoclonus and myoclonus and had some improvement. She also received 2 doses of intravenous rituxan (1 g, with the same dose repeated after 4 months) and again had some mild improvement in her symptoms. However, the patient had the most improvement after she was prescribed an C1-esterase inhibitor (human) (Berinert), with 500 U administered intravenously twice weekly. After 4 C1-esterase inhibitor infusions, the patient's symptoms of edema, recurrent migraines, severe fatigue, vision, and balance problems resolved almost completely and did not recur for the last 5 months she was undergoing treatment. She has reported a marked improvement in her overall quality of life and has been able to continue her studies in medical school.

Patient 2 was diagnosed with HAE type 1 at 48 years of age, but the patient reported that her attacks had been ongoing intermittently for years, with continued swelling of her face, abdomen, knees, and elbows, resulting in extreme discomfort and affecting her ability to work and her quality of life. Further symptoms included red painful rashes, severe migraine headaches, hearing loss, tinnitus, and dizziness, as well as nausea and vomiting. These symptoms did not respond to steroids, antihistamines, IVIG infusions, or omalizumab and had resulted in visits to numerous medical specialists and numerous emergency department visits with no improvement. In January 2014, the patient applied for disability because she was unable to work, illustrating how severe and pervasive her symptoms were. The patient underwent brain MRI on 2 separate occasions, but the imaging only revealed minimal white matter changes in the frontal lobes of dubious clinical significance. She was evaluated for HAE based on her abdominal