

Symptoms of immediate chlorhexidine hypersensitivity in patients with a positive prick test

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There are numerous reports of anaphylaxis from chlorhexidine in surgical operations and other medical procedures, usually due to its application to wounds or mucous membranes. We wanted to analyse the clinical data of patients with a positive chlorhexidine prick test and perform some additional testing. We studied the case records of the patients with a positive chlorhexidine prick test and performed an open application test and tests for specific IgE. We found 33 patients with a positive prick test. 10 of them had had severe symptoms from chlorhexidine, and 11 had had only mild local symptoms. The size of the prick test reaction was mainly in line with the strength of the severest symptoms. Small 3- to 4-mm reactions were usually without obvious clinical relevance. Specific IgE could be demonstrated in 6 patients out of 14 tested by the ImmunoCAP™ method. Besides severe attacks, patients with a positive prick test often have milder local symptoms, such as exacerbation of dermatitis. Local symptoms from chlorhexidine-containing products may precede severe attacks. We recommend a prick test to be performed routinely when symptoms during medical interventional procedures, e.g. local and general anaesthesia, are investigated.

Key words: anaphylaxis; contact urticaria; ImmunoCAP™; immunospot; open application test; prick test; specific IgE. © Blackwell Munksgaard, 2006.

Accepted for publication 13 April 2006

Chlorhexidine (1,1'-hexamethylenebis[5-(*p*-chlorophenyl)biguanide]) is an antiseptic that is widely used as digluconate (CAS 18472-51-0) and diacetate (CAS 56-95-1) salts in solutions, creams, gels, and wound dressings. Chlorhexidine is used to disinfect the skin and mucous membranes prior to surgical operations and to treat wounds and cutaneous and oral infections. Chlorhexidine creams and gels are used as lubricants in urethral catheterization and gynaecological and endoscopic examinations. Chlorhexidine is also used in contact lens solutions and acne preparations and as a preservative in cosmetics and personal care products.

Since 1986, there have been numerous reports of anaphylaxis and other serious symptoms of immediate hypersensitivity (1, 2). These have typically appeared in surgical operations, wound cleansing, cystoscopy, urethral catheterization, or insertion of chlorhexidine-impregnated central venous catheters (2). There are several reports of chlorhexidine-specific IgE in patients with symptoms of immediate hypersensitivity (3–6). In addition to immediate hypersensitivity, chlorhexidine is also a cause of delayed contact allergy, although

reports of allergic contact dermatitis are not very numerous (7).

In the Skin and Allergy Hospital, chlorhexidine gluconate has been included in routine prick test series of 'local anaesthetics' and 'general anaesthetics' since 1995, and since 1998 also in the series of 'cosmetics' and 'hair cosmetics'. So, a relatively large number of patients without a specific suspicion of immediate chlorhexidine hypersensitivity have been tested. We wanted to analyse the clinical data of the patients with a positive prick test and perform some additional testing, an open application test and detection of specific IgE.

Patients and Methods

In the Skin and Allergy Hospital of the Helsinki University Central Hospital, chlorhexidine digluconate has been prick tested since January 1995. The concentration was first 1% in aqua, and then decreased to 0.5% aqua in January 1998.

The case records of all patients with a positive prick test reaction (at least 3 mm) to chlorhexidine were retrieved. Data about their use of

Table 1. Patients with a positive skin prick test to chlorhexidine, test results, symptoms from chlorhexidine products, the corresponding product and the indication for its use

Patient No.	Age (years), sex	Prick test (mm) 1% concentration	Open application	ImmunoCAP (kU/l)	Symptoms from chlorhexidine (When no symptoms, indication for chlorhexidine prick)	Product	Medical procedure
1	25, F	5	ND	ND	Generalized urticaria	Hibitane [®] cream	Gynaecological examination
2	58, M	6	–	4.2	Generalized urticaria	Skin disinfectant	Urologic operation
3	22, F	12 + Ps	ND	<0.35	Immediate itching Dyspnoea, undefined skin eruption Facial erythema	Sibicort [®] cream Skin disinfectant Clerasil [®] solution	Treatment of dermatitis Knee operation Treatment of acne
4	15, F	7	–	ND	Exacerbation of dermatitis Urticaria and skin oedema Erythema Uncomfortable feeling on the genitals	Sibicort [®] cream Skin disinfectant Clerasil [®] solution Cream	Treatment of dermatitis Appendectomy Acne treatment Gynaecological examination
5	30, M	11	–	0.28	Erythema and skin oedema, malaise Undefined skin eruption Erythema and 'burning' on application site	Skin disinfectant Skin disinfectant Sibicort [®] cream	Conducting pathway ablation Hearth catheterisation Treatment of dermatitis
6	69, F	6	–	<0.35	Generalized urticaria	KY [®] -gel	Colonoscopy
7	41, M	7	–	0.43	Lingual oedema 2–3×	Mouthwash	Dental Treatment
8	12, M	10	ND	ND	Asthma, undefined skin eruption	Mouthwash	Orthodontic treatment
9	7, M	4	ND	ND	Cough after skin application, chronic rhinitis	Sibicort [®] cream	Treatment of dermatitis
10	14, M	6	ND	ND	Exacerbation of dermatitis	Sibicort [®] cream	Treatment of dermatitis
11	8, M	10	ND	ND	Exacerbation of dermatitis	Sibicort [®] cream	Treatment of dermatitis
12	13, M	5	–	<0.35	Immediate exacerbation of dermatitis, skin oedema	Sibicort [®] cream	Treatment of dermatitis
13	22, F	5	ND	0.72	Immediate exacerbation of dermatitis	Sibicort [®] cream	Treatment of dermatitis
14	33, M	8	–	2.1	Immediate exacerbation of dermatitis	Sibicort [®] cream	Treatment of dermatitis
15	32, F	6	–	<0.35	Exacerbation of dermatitis	Sibicort [®] cream	Treatment of dermatitis
16	51, F	3	–	<0.35	Exacerbation of hand dermatitis	Disinfectants	Hand disinfection
17	53, F	8	ND	ND	No symptoms (Suspicion of local anaesthetics allergy)	–	
18	1, M	3	ND	ND	No symptoms (Suspicion of vaccine allergy)	–	
19	29, M	4	ND	ND	No symptoms (Atopic dermatitis)	(Sibicort [®] cream)	(Treatment of dermatitis)
20	50, F	3	ND	ND	No symptoms (Suspicion of local anaesthetics allergy)	–	
21	62, F	3	ND	ND	No symptoms (Suspicion of local anaesthetics allergy)	–	
22	30, F	3	ND	ND	No symptoms (Asthma)	(Disinfectants)	(Hand disinfection)
23	32, M	0.5% concentration 10 + ps.	–	1.2	Generalized urticaria	Skin disinfectant	Knee operation

time span could neither be determined in those 13 patients (nos. 17–22 and 27–33) who had had no symptoms from chlorhexidine products.

An open application with 1% and 5% chlorhexidine digluconate was performed in 13 patients (Table 1) at an average of 30 months (range 1–68 months) after the positive prick test. The test was negative in all patients. 3 patients could not be reached and 4 could not be tested because of pregnancy, dermatographism, dermatitis on the test site, or antihistamine use.

Specific IgE was determined in the sera of 14 patients at an average of 29 months (range 1–61 months) after the positive prick test. The results of ImmunoCAP™ are given in Table 1. The same sera were negative in the immunospot assay.

Discussion

There is no universally accepted clinical definition of anaphylaxis (10). The European Academy of Allergology and Clinical Immunology (EAACI) nomenclature task force has proposed a broad definition: a severe, life-threatening, generalized, or systemic hypersensitivity reaction (11), but they did not further define the terms severe, life threatening, generalized, or systemic. None of our patients had anaphylactic shock with cardiovascular collapse. 10 of our patients (nos. 1–9 and 23) had severe symptoms, which can be classified under the broad definition of anaphylaxis. Most of these attacks were objectively documented. Many patients in this group had also experienced mild symptoms, such as erythema, exacerbation of dermatitis, or only subjective uncomfortable feeling, from, e.g. acne preparations and chlorhexidine-containing creams prior to the severe symptoms during a medical procedure, which lead to the diagnosis of chlorhexidine allergy. In the group, 6 patients had a specific suspicion of chlorhexidine hypersensitivity, but in 3 patients, the positive reaction to chlorhexidine was shown by testing in the 'local anaesthetics series' and in 1 by testing the 'general anaesthetics series'.

The second group of 11 patients (nos. 10–16 and 24–26) had had only local exacerbation of dermatitis from topical chlorhexidine. These symptoms were anamnestic data and not based on any objective documentation. However, several patients in this group had large prick test reactions and 2 patients also had specific IgE.

In a recent literature review on immediate chlorhexidine hypersensitivity, all but 1 of the 66 cases reviewed had severe symptoms, hypotension, anaphylactic shock, respiratory symptoms, or generalized urticaria, and the single remaining case was local contact urticaria of the hands (2). Our series shows that the clinical spectrum of immediate

chlorhexidine hypersensitivity also includes cases with milder local skin symptoms on the application site of a chlorhexidine-containing product. These mild symptoms are not necessarily always specific, but it is also difficult to notice small wheals, especially on eczematous skin. The patients with mild symptoms are possibly at risk for more serious generalized symptoms, if chlorhexidine is applied to their mucous membranes or wounds.

12 of our patients (nos. 17–22 and 27–33) had no symptoms consistent with immediate hypersensitivity to chlorhexidine. In this group, the prick test usually gave only suggestive 3- to 4-mm-large reactions. In 2 patients, the test was repeated and found negative in the second time (nos. 19 and 20 in Table 1). These reactions were probably mostly unspecific irritant reactions. The 0.5% concentration also gave these small reactions. According to a recent literature review, 0.005%–0.2% aqueous solution does not lead to unspecific results (2). Some relevant reactions may be lost with the lower concentrations (12). In our hospital, the absolute proportion of positive reactions decreased when the test concentration was lowered from 1% to 0.5%. At the same time, the indications for prick testing had become much wider, so the true effect of the concentration is difficult to evaluate. However, the number of small reactions did not decrease. In our series, the size of the wheal was mostly in line with the relevance and severity of the symptoms.

In a recent report, a patient with anaphylaxis was negative on prick testing with 0.01% solution, but open application with a 1% solution was positive in 15–20 min (12). All our 13 open application tests remained negative even with the high 5% concentration. The result might have been different, if the tests were performed soon after the presenting symptoms. In 1 patient, the test site was rubbed vigorously with 5% solution, and wheals appeared soon after the skin was visibly broken. Our result is consistent with the Swedish experience that provocation of wheals needs a slightly damaged skin (13). In 2 other previous case reports, an open application test showed wheals after 1 hr when applied to normal skin (1, 14). We did not notice any late reactions.

Specific IgE could be demonstrated by the ImmunoCAP™ method in the sera of only 6 patients. The sera were taken long after the diagnosis of chlorhexidine hypersensitivity. The number of positive tests would probably have been greater, if the sera were taken a few months after the presenting symptoms. The general rule is that blood samples for testing with drug ImmunoCAP™ should not be collected later than 6 months after the adverse reaction. The experimental

prototype reagents were not fully validated. 4 of the patients with positive sera had had severe symptoms, but 2 had had only exacerbation of dermatitis from topical chlorhexidine cream. In the immunospot, IgE antibodies were not detectable to chlorhexidine hapten or its simple incubation complex with human serum albumin. Obviously, more laborious chemical reactions are needed to form a covalent hapten–protein complex. Currently, the determination of specific IgE is only a supplemental test for investigation of immediate chlorhexidine allergy.

In summary, in addition to the well-known anaphylactic reactions, the clinical spectrum of immediate chlorhexidine hypersensitivity also includes milder local skin symptoms from topical application. Large prick tests reactions to 0.5%–1% chlorhexidine digluconate were usually connected with relevant immediate symptoms from chlorhexidine. Some patients had also experienced mild local symptoms from chlorhexidine products prior to the severe attack that lead to diagnosis. The 0.5%–1% test concentrations also produced many small 3- to 4-mm-wide reactions that were clinically irrelevant and probably irritant reactions. An open application test with 5% chlorhexidine to intact skin remained negative in our patients. Mild local symptoms from chlorhexidine-containing products may precede severe attacks. We recommend a prick test to be performed routinely when symptoms during medical interventional procedures, e.g. local and general anaesthesia, are investigated.

Acknowledgements

We thank Pharmacia Diagnostics for the determination of specific IgE and the Finnish Society of Allergology and Immunology for financial support.

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