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***Dynamics of plasma levels of specific IgE in chlorhexidine allergic patients
with and without accidental re-exposure***

Running head: specific IgE in chlorhexidine allergy

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Abstract

Background

Chlorhexidine is an effective disinfectant, which may cause severe allergic reactions. Plasma level of specific IgE to chlorhexidine (ImmunoCAP®) has high estimated sensitivity and specificity when measured within six months of allergic reaction, but knowledge of the dynamics over longer time periods is lacking and it is unknown whether levels fall below $<0.35\text{kUA/l}$ in patients with previously elevated levels. It is also unclear whether re-exposure influences levels of specific IgE.

Objective

To investigate the dynamics of specific IgE in chlorhexidine allergic patients with and without re-exposure.

Methods

All patients diagnosed with chlorhexidine allergy in the Danish Anaesthesia Allergy Centre January 1999 to March 2015 were invited to participate. The study included blood samples from the time of reaction and time of investigation and blood samples drawn prospectively over several years.

Results

Overall, 23 patients were included. Specific IgE within hours of reaction was available in eight patients and was $>0.35\text{kUA/l}$ in six of these. During allergy investigations, usually two to four months later, specific IgE was $>0.35\text{kUA/l}$ in 22 of 23 patients. In the following months/years specific IgE declined $<0.35\text{kUA/l}$ in 17 of 23 patients (most rapidly within four months). Nine re-exposures in the healthcare setting were reported by seven patients (35%). Most re-exposures caused symptoms and was followed by an increase in specific IgE. Two patients with specific IgE $<0.35\text{kUA/l}$ reacted upon re-exposure.

Conclusions & Clinical relevance

Time from reaction should be considered when interpreting specific IgE-results. Specific IgE is $>0.35\text{kUA/l}$ in most patients at time of reaction but should be repeated after a few weeks/months if negative. The optimal sampling time seems to be >1 month and <4 months. A value $<0.35\text{kUA/l}$ neither excludes allergy nor implies loss of reactivity in previously sensitized patients. Re-exposures

are common, often iatrogenic, and can cause a rebound in specific IgE.

Introduction

Chlorhexidine is a highly effective disinfectant^{1,2} and is widely used in the healthcare setting in many countries³. Although most people tolerate chlorhexidine well, it can cause severe allergic reactions such as urticaria, anaphylactic shock or even cardiac arrest^{4,5}. In 2007, an IgE-mediated mechanism behind chlorhexidine allergy was confirmed⁴.

The Danish Anaesthesia Allergy Centre (DAAC) is the national reference centre for investigation of patients with perioperative allergic reactions. During surgery, exposure to chlorhexidine can be extensive and consequently chlorhexidine allergic patients have a high risk of reacting in this setting. In DAAC, all referred patients are tested with chlorhexidine as part of the investigations and approximately 10% are diagnosed with chlorhexidine allergy⁶. Two recent studies from the UK showed that 5% of patients with suspected perioperative allergic reactions and 7% of patients with verified perioperative allergic reactions, respectively, tested positive to chlorhexidine^{7,8}.

In DAAC, the diagnosis of chlorhexidine allergy is based on a relevant clinical history in combination with results of skin prick test, intradermal test, specific IgE (ImmunoCAP®, Thermo Fisher Scientific, Uppsala, Sweden) and in some cases histamine release test (HR-test) (Reflab Aps, Copenhagen Denmark).

The prevalence of positive specific IgE to chlorhexidine in the general population is unknown, but based on data from patients investigated in DAAC, it was recently estimated that both sensitivity and specificity of specific IgE to chlorhexidine are high (100% and 97%, respectively)⁶. Notably, in that study samples were collected within six months as recommended by the manufacturer⁹. It has previously been shown that plasma levels of specific IgE decrease over time for chlorhexidine⁴ and other non-protein allergens such as ethylene oxide and penicillins¹⁰⁻¹², but the dynamics of specific IgE to chlorhexidine over longer time periods have never been investigated. Currently, it is unknown

whether specific IgE will eventually drop below the recommended cut-off of 0.35kUA/l on lack of exposure in patients with previously elevated levels, as described for penicillins¹². It is also unclear whether re-exposure to chlorhexidine influences specific IgE-values.

The aim of this study was to follow the dynamics of plasma levels of specific IgE to chlorhexidine over time in patients with chlorhexidine allergy with and without known re-exposure to chlorhexidine.

Methods

The local Human Ethics Research Committee approved the study protocol (project ID H-3-2012-144).

Patients

Inclusion criteria:

- Patients diagnosed with chlorhexidine allergy during investigation for a suspected perioperative allergic reaction in the Danish Anaesthesia Allergy Centre (DAAC) from January 1999 to March 2015
- Aged ≥ 18 years and still alive at time of inclusion

Overall 44 patients were diagnosed with chlorhexidine allergy in DAAC from January 1999 to March 2015. Of these, 11 had died and one was below 18 years at time of inclusion. Of the 11 patients who had died (nine men and two women, median age 60 years [range 38-86 years]) nine were investigated from 1999 to 2005. Most were gastrointestinal patients (n=6) or urological patients (n=2) and suffered from a malignant disease. Consequently, 32 patients fulfilled the inclusion criteria and were invited to participate and were included from January 2013 to March 2015.. Invitations included a letter with information about the project and a consent form. Those not responding within a few months were contacted by telephone. Patients not responding to the telephone call were not contacted further.

Controls

All patients in DAAC are tested for chlorhexidine allergy with skin prick test, intradermal test, specific IgE and in some patients histamine release test. A total of 23 non-chlorhexidine allergic patients investigated for a suspected perioperative allergic reaction in DAAC from January 1999 to March 2015 were included as controls. Controls were matched with patients with respect to age and sex.

Study design

Data on age, sex, reaction class and type of surgery performed were collected from the clinical database hosted in the department and from case notes. Reaction classes were defined as in previous manuscript using a modified version of the Ring and Messner classification^{6, 13}: Class 1: mild reactions with generalized cutaneous signs, self-limiting. Class 2: moderate reactions with multi-organ involvement, may be self-limiting. Class 3: severe life-threatening reactions, usually multi-organ involvement, requires specific treatment. Class 4: cardiac arrest.

This study included blood samples drawn within one to three hours of the reaction and at the time of investigation in DAAC as well as blood samples drawn for the purpose of this study. Sera were analysed for specific IgE for chlorhexidine (Immunocap®, Thermo Fisher Scientific, Uppsala, Sweden) applying a cut-off of 0.1kUA/l, and total IgE.

Blood samples from time of reaction and time of investigation

These included: a) a blood sample for tryptase analysis drawn within one to three hours of the reaction leading to referral to DAAC, b) a blood sample drawn after initial patient contact four to six weeks later and c) a blood sample drawn at time of investigation in DAAC, usually two to four months after the allergic reaction.

In our laboratory, values are normally reported as <0.35kUA/l and, if lower, absolute values are not available. Consequently, for retrospective blood samples with a specific IgE <0.35kUA/l, we had to re-analyse samples using a cut-off of 0.1kUA/l. If not already available, specific IgE for chlorhexidine

was measured on all retrospective blood samples for both patients and controls.

Blood samples drawn prospectively for this study

As it has previously been shown that levels of specific IgE decline over time, it was decided to draw blood samples more frequently from patients with a recent reaction than from those with a reaction long ago. For patients who reacted less than two years prior to inclusion, four annual blood samples were collected; patients reacting two to four years prior to inclusion had two annual blood samples collected; patients reacting more than four years prior to inclusion had one annual blood sample collected.

Serum was kept at -20°C and all analyses were performed in September to December 2015.

Patient follow-up

At the end of the study all included patients were contacted by telephone and asked whether they had been accidentally re-exposed to chlorhexidine after the diagnosis. Those not responding had a letter asking them to contact the investigators. The time of re-exposure, the product used during re-exposure and allergy symptoms were noted.

Statistics

The data were processed with SPSS (SPSSTM Statistics, Chicago, IL, USA; IBM PASW Statistics) for WindowsTM, edition 22.0 and Microsoft Excel.

Results

Informed consent was obtained from 23 of the 32 patients who fulfilled the inclusion criteria. Seven patients declined participation and two did not respond to letter nor telephone calls. Of the 23 patients, data from 15 had been included in a previous study evaluating the tests in chlorhexidine allergy⁶. Demographic data and details on reaction class and type of surgery performed at the of time allergic reaction for the 23 patients can be seen in table 1. Of the 23 patients, 18 reactions (78%) were graded as class 3 (anaphylaxis) and only five reactions (22%) were graded as class 1 or 2.

In comparison, of all 462 patients investigated in DAAC from 2004 to 2015, 251 (54.3%) reactions were graded as class 1 or 2, 195 (42.2%) were graded as class 3 and 16 (3.5%) were graded as class 4, indicating that chlorhexidine allergic patients have comparatively more severe reactions.

A total of 114 blood samples (retrospective and prospective) from the 23 patients and 23 controls were included in the study. Due to highly variable initial values and variable dynamics, graphical representation of all results is not meaningful, but all specific IgE-values can be found in appendix 1.

Specific IgE at time of reaction and dynamics in subsequent weeks/months

Overall, six of eight patients had a specific IgE >0.35 kUA/l in a blood sample drawn within one to three hours of the initial reaction with values ranging from 0.51 to 66.7kUA/l. In seven of eight patients, specific IgE increased over the subsequent weeks/months.

Specific IgE was >0.35 kUA/l in 22 of 23 patients at time of investigation in DAAC a median of 10 weeks after the allergic reaction including all eight patients with a blood sample available from time of reaction. In contrast, specific IgE was <0.35 kUA/l in all 23 controls and <0.1 kUA/l in 18 of these (data not shown). The five controls with a detectable specific IgE >0.1 kUA/l had values of 0.12, 0.13, 0.15, 0.18 and 0.24kUA/l, respectively and total IgE was 239, 716, 1235, 957 and 1252 kIU/l, respectively.

Dynamics of specific IgE over time in patients with no known re-exposure

To illustrate the dynamics of specific IgE in the time after the reaction, we have selected one patient with many blood samples available and no known re-exposure (figure 1).

Figure 1 shows that specific IgE increased in the first months but then declined and eventually fell <0.35 kUA/l after two to three years in this patient. In 21 of 23 patients, lower values were measured in blood samples drawn at the end of this study compared with values measured during the initial investigations. Indeed, 17 of 23 patients had a specific IgE-value <0.35 kUA/l measured at some point during the study and seven of these also had values <0.1 kUA/l. Shortest interval from allergic reaction to a measured specific IgE-value <0.35 kUA/l was four months (patient 11) and shortest

interval to a value $<0.1\text{kUA/l}$ was 64 months (patient 11). The rate of decline seemed to vary greatly between patients. Specific IgE remained above 0.35kUA/l for many years without a known re-exposure in four patients (patients 7, 8, 10 and 13).

Dynamics of specific IgE over time in patients with known re-exposure

During follow-up to identify accidental re-exposures, 20 of 23 patients responded. Of these, seven patients (35%) reported a total of nine accidental re-exposures - all in the healthcare setting. Seven of the nine re-exposures were symptomatic.

Re-exposures during surgery

Three patients were re-exposed to chlorhexidine during surgery and all three developed anaphylactic shock (patients 3, 5 and 18). Specific IgE-values were available from blood samples drawn in close relation to the re-exposures for patients 5 and 18, but not for patient 3, as illustrated in figure 2a and 2b. Both re-exposures were followed by an increase in specific IgE.

Re-exposures in urethral gels

Two patients were re-exposed to chlorhexidine in a urethral gel: one reported local itching and swelling although specific IgE was 0.24kUA/l one year earlier and 0.21kUA/l two months after the exposure (patient 15); another reported that re-exposure did not result in symptoms but specific IgE had increased in subsequent blood sample (patient 19) (see figure 2C).

Re-exposures in skin swabs

Four patients reported re-exposure to chlorhexidine in skin swabs: one developed anaphylactic shock and a subsequent increase in specific IgE (patient 18, figure 2B); another developed local symptoms only and specific IgE was $<0.1\text{kUA/l}$ one year later (patient 5, figure 2A); a third reported general discomfort and redness of skin (patient 23); a fourth reported that exposure did not cause symptoms (patient 2). The two latter patients did not have any blood samples available in close

relation to the exposures.

Discussion

The focus of this study was to investigate the dynamics of specific IgE to chlorhexidine over time in 23 chlorhexidine allergic patients with and without re-exposure to chlorhexidine.

Specific IgE was $>0.35\text{kUA/l}$ in most blood samples drawn within one to three hours of the reaction and an increase was observed over subsequent weeks/months. It has been shown previously by our group in 2007 that specific IgE may be elevated at the time of initial reaction and this has been confirmed for other allergens e.g. ethylene oxide and neuromuscular blocking agents^{11,14}.

Consequently, specific IgE is not consumed entirely during the allergic reaction as previously thought but can be measured in serum in most patients at time of reaction. However, if negative, the test should be repeated after a few weeks/months as specific IgE is likely to increase.

After the initial increase, specific IgE gradually declines and eventually falls below 0.35kUA/l in most patients. In this study, the rate of decline varied considerably between patients with most rapid decline below 0.35kUA/l at four months. This may indicate that measuring specific IgE to chlorhexidine within six months of the allergic reaction, as recommended by manufacturer, is too late in some patients. However, four patients still had elevated levels of specific IgE above 0.35kUA/l many years after the allergic reaction, although they denied re-exposure. It is not possible to predict how long specific IgE to chlorhexidine will remain elevated in a patient, and this is in line with previous findings on penicillin allergy¹².

In an earlier manuscript, we recommended that testing for chlorhexidine allergy should include specific IgE and skin prick test as a minimum⁶. However, as shown above, specific IgE results should be interpreted with caution when investigations take place a long time after the allergic reaction. Therefore, in these patients, supplementation of diagnostic testing with intradermal test could be considered. However, currently, it is unknown how long skin tests remain positive and this should be the focus of future studies.

Accepted Article

It has previously been speculated that a lower cut-off of specific IgE to chlorhexidine could be used to increase the diagnostic accuracy^{15,16}. In this study, we found that in most patients with a specific IgE-value <0.35kUA/l, initially specific IgE was still >0.1kUA/l. However, in patients with the longest intervals between initial reaction and inclusion in this study, specific IgE-values did decrease to <0.1kUA/l. Consequently, it seems unlikely that values <0.35kUA/l can be used clinically to differentiate between those with the allergy and those without. It has previously been shown for Rocuronium that total IgE over 1,500kIU/l could interfere with results in the ImmunoCAP system¹⁷. However, in all the five controls with a specific IgE above 0.1kUA/l, total IgE was below 1,500kIU/l. Chlorhexidine is widely used in the healthcare setting. As a consequence, there is a high risk of re-exposure, and several case reports have described patients with immediate-type chlorhexidine allergy, who were accidentally re-exposed^{5,18,19}. In the current study, seven patients (35%) reported a total of nine re-exposures in the healthcare setting and the highest risk of re-exposure seems to be in the perioperative setting, in urethral gels and in skin swabs.

Most re-exposures caused symptoms and an increase in specific IgE. However, some re-exposures resulted in symptoms only with no increase in specific IgE, while others were asymptomatic but was followed by an increase in specific IgE. Our study shows that patients can still develop symptoms when specific IgE is below 0.35kUA/l and therefore a value below 0.35kUA/l does not necessarily indicate loss of reactivity. This finding is in line with penicillin allergy, where it was recently shown that some patients with specific IgE below 0.35kUA/l are still allergic whereas others tolerate the drug on subsequent drug provocation¹². One could speculate that in the time leading up to surgery, patients are exposed repeatedly over a relatively short time e.g. through blood taking and investigations prior to surgery. Each of these exposures may provoke an increase in specific IgE, making a serious reaction more likely to occur upon the extensive exposure that often takes place perioperatively.

Besides being used as a disinfectant in the healthcare setting, chlorhexidine can also be used as a

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preservative in cosmetic products²⁰. Although chlorhexidine in cosmetic products has been reported to cause contact allergy^{21,22}, it very rarely, if ever, causes immediate-type allergic reactions. To our knowledge, no case reports have ever been published of patients with immediate-type reactions caused by chlorhexidine in cosmetics. It has been reported that chlorhexidine does not penetrate intact skin²³, but it is unclear whether an exposure through cosmetic products on broken skin or a mucous membrane may cause allergic sensitization or an increase in specific IgE in already sensitized individuals. Indeed, for some patients included in this study, specific IgE did increase at times where patients denied re-exposure and perhaps unknown exposure in cosmetics or in the healthcare setting could play a role.

Old studies suggest that the half-life of the IgE molecule in plasma is in the order of few days²⁴. Thus IgE measured months apart must be newly synthesized. It could be hypothesized that after re-exposure to chlorhexidine there is an induction phase of one to three weeks where memory B-cells are expanded after which plasmablasts produce large amounts of IgE. Short-lived plasmablasts soon die, causing an initial rapid decline in plasma IgE level. Few long-lived plasmablasts migrate to the bone marrow or other permanent compartments where they continue their IgE production for extended periods in many cases maintaining measurable IgE for months or years. It is possible that non-protein allergens stimulate relatively more short-lived plasmablasts and thus induce more short-lived IgE-response compared to protein allergens inducing insect venom, food or inhalation allergies.

In conclusion, most patients with chlorhexidine allergy have a specific IgE above 0.35kUA/l at the time of reaction, and levels increase in the weeks/months after the allergic reaction. Subsequently specific IgE gradually declines below 0.35kUA/l on lack of exposure, but this does not prove loss of reactivity. This highlights the importance of taking time elapsed from the allergic reaction into consideration when interpreting specific IgE-results. The optimal sampling time seems to be >1 month and <4 months. Accidental re-exposures are surprisingly common, in this study 35% of

patients with confirmed chlorhexidine allergy reported re-exposure in the healthcare setting, both symptomatic and asymptomatic. This highlights that healthcare workers need to be aware of possible sources of exposure when managing patients with chlorhexidine allergy and emphasizes the need to consider chlorhexidine as an allergen in *all* allergic reactions in the healthcare setting.

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Conflicts of interest

MS Opstrup has received research grants from the Aage Bangs Foundation and the Beckett Foundation. H.J. Malling has received research grants to the Allergy Clinic, Gentofte Hospital, Denmark, from the National Institute of Health, EU-commission, Danish Toyota Fund and Tryg Foundation, and is both a consultant and a speaker for ALK-Abello, Denmark and Stallergenes, France. He is also a member of the Danish National Medico-legal Council. LH Garvey has been a speaker for a meeting organized by Thermo Fisher Scientific for laboratory technicians in Denmark and been a consultant for Merck related to allergic reaction during anaesthesia. LK Poulsen and BM Jensen declare no conflicts of interest.

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Patient number	Age years	Sex F/M	Reaction class 1-4	Surgical specialty
1	66	M	3	Urology
2	54	M	3	Ear-Nose-Throat
3	37	M	4	Gastrointestinal
4	40	M	3	Urology
5	27	F	3	Gastrointestinal
6	50	F	3	Gastrointestinal
7	86	M	3	Urology
8	67	M	3	Gastrointestinal
9	68	M	3	Urology
10	47	F	1	Plastic surgery
11	16	M	2	Ear-Nose-Throat
12	32	M	3	Orthopaedic
13	73	M	3	Gastrointestinal
14	32	M	2	Orthopaedic
15	68	M	2	Urology
16	70	M	3	Urology

Patient number	Age years	Sex F/M	Reaction class 1-4	Surgical specialty
17	59	M	2	Urology
18	48	M	3	Back surgery
19	53	M	3	Urology
20	76	M	3	Neurosurgery
21	69	M	3	Urology
22	64	M	3	Urology
23	67	M	3	Gastrointestinal

Table 1. Demographic data and information about the allergic reaction leading to referral to Danish Anaesthesia Allergy Centre.

<i>Patient number</i>	<i>Specific IgE (kUA/l)</i>	<i>Total IgE (kIU/l)</i>	<i>Time from allergic reaction (days)</i>	<i>Re-exposures</i>
1	1.60	ND	71	Unknown
	<0.1	17.1	4370	
	<0.1	15.0	4784	
2	0.49	ND	201	1. Asymptomatic re-exposure in skin swab around day 600
	0.89	69.1	3542	
	<0.1	12.3	3954	
3	3.99	167	83	1. Severe allergic reaction during surgery around day 900
	1.68	ND	159	
	0.41	60.3	2927	
	0.27	238	3339	
	0.38	150	3612	
4	<0.35*	373	127	No known re-exposure
	0.11	729	163	
	<0.1	350	2976	
5 Data presented graphically in figure 2A.	0.24	30.3	0	1. Anaphylactic shock during surgery caused by chlorhexidine around day 180 2. Local redness and itching caused by skin swab around day 2500
	0.74	53.1	122	
	2.96	122	413	
	0.98	109	533	
	<0.1	24.8	2837	
6	1.14	4.63	44	No known re-exposure
	0.89	5.93	89	
	<0.1	8.69	2584	
7	0.29	18.8	0	No known re-exposure
	0.67	36.1	103	
	0.66	46.5	154	
	4.95	155	2556	
8	11.9	769	248	No known re-exposure
	11.7	873	266	
	0.8	253	2761	
	0.69	171	3131	
9	33.7	803	58	Unknown

	22.7	366	149	
	<0.1	9.98	2346	
	0.2	184	2837	
10	5.63	151	185	No known re-exposure
	4.01	101	245	
	0.73	91.4	2081	
	0.59	56.7	2487	
11	0.44	4.7	71	No known re-exposure
	0.18	5.99	121	
	<0.1	5.03	1927	
	<0.1	3.55	2360	
12	2.45	158	22	Unknown
	1.49	86.2	63	
	0.31	78.7	1799	
	0.89	84.2	2206	
13	3.07	34.0	0	No known re-exposure
	7.59	93.2	57	
	1.24	43.7	1423	
	1.03	40.5	1624	
	1.34	47.7	2080	
14	3.76	87.7	84	No known re-exposure
	3.29	80.5	96	
	0.19	169	1429	
	0.15	164	1831	
15	0.51	462	0	1. Re-exposure in urethral gel causing local itching around day 1570
	0.83	527	28	
	0.25	453	998	
	0.24	398	1148	
	0.21	275	1631	
16 Data presented graphically in figure 1.	1.45	47.1	0	No known re-exposure
	5.19	182	50	
	4.89	181	55	
	2.52	119	196	
	1.14	130	750	
	0.47	75.8	846	
	0.33	100	994	
	0.26	93.4	1079	
	0.26	84.5	1178	
	0.26	77.2	1444	
17	0.51	91.2	37	No known re-exposure
	0.52	113	105	
	0.44	95.0	160	
	0.37	99.4	677	
	0.57	91.3	779	
	0.47	115	890	
	0.37	159	923	
	0.34	101	1099	
	0.37	73.6	1335	
18 Data	2.17	ND	40	1. Anaphylactic shock caused by
	2.17	81.4	66	

presented graphically in figure 2B.	5.53	95.4	70	chlorhexidine during surgery at day 40 2. Anaphylactic shock caused by chlorhexidine in skin swab at day 277
	3.95	73.7	83	
	1.66	ND	277	
	2.33	84.5	326	
	0.31	283	437	
	0.9	48.5	529	
	0.96	74.0	643	
	1.04	76.0	676	
	0.73	61.3	852	
19 Data presented graphically in figure 2C.	0.19	62.6	-92**	1. Asymptomatic re-exposure in urethral gel during surgery at day 299
	1.67	45.4	31	
	0.65	59.9	250	
	0.99	83.1	340	
	0.29	47.1	493	
20	0.74	46.0	190	No known re-exposure
	0.65	47.1	193	
	0.58	34.4	196	
	0.34	65.0	473	
	0.22	81.1	608	
	0.15	62.0	694	
	0.23	121	951	
21	5.29	ND	0	No known re-exposure
	8.7	506	138	
	0.16	546	173	
22	66.7	516	0	No known re-exposure
	163	656	16	
	98.6	1008	26	
	126	756	109	
	42.7	558	195	
	25.7	328	355	
23	14.5	158	0	1. General discomfort and redness of skin caused by skin swab around day 240
	16.8	161	5	
	12.1	169	9	

Appendix 1. Table of all included patients' test results. *Not enough serum to re-analyse sample. ** A blood sample drawn 92 days before the allergic reaction was available in this patient. ND=Not done.







