The relevance of chlorhexidine contact allergy

Jussi Liippo[1], Päivi Kousa[2] and Kaija Lammintausta[1]

[1] *Department of Dermatology, Turku University Hospital, 20521 Turku, Finland and* [2] *The Helsinki Asthma and Allergy Association in Finland, 00270 Helsinki, Finland*

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Summary

Background. Chlorhexidine is used for disinfection of skin and mucosae in medicine and dentistry. Prolonged exposure may lead to contact sensitization and allergic contact dermatitis or stomatitis.

Objectives. The purpose of this study was to analyse the sources of chlorhexidine exposure and sensitization, and to obtain data on the prevalence of sensitization and chlorhexidine-related contact allergy.

Patients and methods. From 1999, patch testing was performed with chlorhexidine digluconate (0.5% aq.) on 7610 general dermatology patients with suspected contact allergy at the Turku University Hospital Dermatology Department. The medical records were reviewed concerning the patients' exposure to chlorhexidine.

Results. A positive patch reaction to chlorhexidine was seen in 36 patients (0.47%). Current dermatitis or stomatitis caused by chlorhexidine-containing topical medicaments was seen in 5 patients. Chlorhexidine sensitization contributed to the current dermatitis in 11 patients. A history of earlier exposure to chlorhexidine-containing products was recalled by only 16 sensitized patients, whereas no exposure was revealed in 4 cases.

Conclusions. Chlorhexidine-containing corticosteroid creams, skin disinfectants and oral hygiene products are principal sources of chlorhexidine contact sensitization. Exposure to chlorhexidine in cosmetics may lead to delayed improvement of eczema in sensitized patients, emphasizing the importance of identifying the potential cosmetic sources.

Key words: allergic contact dermatitis; chlorhexidine; contact sensitization; skin and mucosa disinfection.

As a cationic diacetate or digluconate salt, chlorhexidine is bactericidal against gram-positive and gram-negative bacteria. It also has bacteriostatic action in low concentrations, and is active against some bacterial spores and viruses. In addition to bacteria, chlorhexidine also has antifungal activity, which can be used to reduce the amount of, for example, skin-colonizing yeasts, including *Malassezia* and various *Candida* species. Chlorhexidine is commonly used for skin and mucosal disinfection in medicine and dentistry. Oral hygiene products, topical therapies and cosmetics include chlorhexidine salts as biocides or preservatives.

IgE-mediated chlorhexidine allergy may lead to type I allergic reactions, extending from mild local symptoms to anaphylaxis in persons with previous immediate-type sensitization (1–6). Chlorhexidine-induced delayed contact sensitization has been reported in adults (7–9) and in children with atopic dermatitis (10), and following prolonged use of topical antiseptic solutions containing chlorhexidine (9).

We have analysed the occurrence of contact sensitivity to chlorhexidine among patients being investigated for contact allergy. The potential and probable sources

Correspondence: Jussi Liippo, Department of Dermatology, Allergy Unit, Turku University Hospital, P.O. Box 52, 20521, Turku, Finland. Tel: +358 2 313 1616; Fax: +358 2 313 1610. E-mail: jussi.liippo@utu.fi

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of sensitization were analysed, including exposure to chlorhexidine in cosmetics.

Materials and Methods

Patch testing

An aqueous solution of chlorhexidine digluconate (0.5%) (Chemotechnique Diagnostics, Vellinge, Sweden) was patch tested in 7610 patients from 1999 to 2009. The European baseline series and one or more additional series, if needed, were tested in each patient. A filter paper in the Finn Chambers® (Epitest Ltd, Tuusula, Finland) was moistened with the aqueous test substance (15 μl) immediately before the application. The chambers were fastened with Scanpor® tape (Norgesplaster A/S, Vennesla, Norway) and removed after 2 days (D2). The reactions were read and interpreted 1–3 days after the removal (D3, D4 or D5) of the chambers according to the generally accepted criteria of the International Contact Dermatitis Research Group (11).

Sources of exposure to chlorhexidine

The relevance of the positive chlorhexidine reactions was retrospectively evaluated on the basis of available clinical data.

Pharmacy products that contain chlorhexidine are listed in the Finnish Pharmaca Fennica catalogue. In addition, information on various other antiseptic over-the-counter products containing chlorhexidine can be obtained from internet resources and company-based databases available in pharmacies.

The Helsinki Asthma and Allergy Association in Finland collects data on all components of cosmetic products marketed in Finland. Data files of sensitizing components in approximately 80% of cosmetic products marketed in Finland are collected yearly. The chemist of the society (M.K.) collected all of the chlorhexidine data for this study.

Results

Chlorhexidine sensitization among dermatology patients and its relevance

Positive patch test reactions to chlorhexidine gluconate were seen in 36 patients (0.47%) aged 13–84 years (Table 1). The primary diagnosis was atopic dermatitis in 8 patients and chronic nummular dermatitis in 6 patients. In general, contact sensitivities were frequent, and allergic contact dermatitis was diagnosed in 14/36 patients. These 14 patients also had multiple other contact sensitivities. For 5 patients, chlorhexidine was the major causative agent (patients 10, 18, 21, 22 and 35 in Table 1), as healing or improvement of the current dermatitis or stomatitis was seen when these patients avoided chlorhexidine. Eleven patients had treated their current dermatitis with chlorhexidine-containing products, indicating recent exposure. Chlorhexidine avoidance, however, did not lead to improvement in these cases. Another 16 patients had a history of occasional exposure that was not related to their current dermatitis. The remaining 4 patients did not report any chlorhexidine exposure.

Concurrent positive patch test reactions were seen in 30/36 patients. Ten patients reacted to perfume mixture(s) and (or) to *Myroxylon pereirae*, and 10 patients also had positive reactions to one or more preservatives used in cosmetics. Reactions to corticosteroids, colophonium and *p*-phenylenediamine occurred in 4 patients each.

Chlorhexidine in marketed products

Aqueous antiseptic preparations for preoperative surgical hand disinfection and for general antiseptic hand washing marketed in Finland generally contain chlorhexidine gluconate 5 mg/ml or chlorhexidine diacetate 0.2 mg/ml. Similar products are also commonly used in preoperative and postoperative skin antisepsis for patients undergoing surgery, and are sold in pharmacies for domestic use.

One medicinal cream is available with 10 mg/g chlorhexidine digluconate and 10 mg/g hydrocortisone (Sibicort®), and another with chlorhexidine digluconate 10 mg/g and hydrocortisone 17-butyrate 1.0 mg/g (Duocort®).

Seven of the numerous mouth washes available in pharmacies contain up to 0.4 mg/ml chlorhexidine gluconate or 0.2–0.1 mg/ml chlorhexidine acetate.

The Helsinki Asthma and Allergy Association gave information to 3500 persons on approximately 8012 cosmetic products between 1999 and 2008. Of these persons, 4.2% (3.0–6.8% yearly) asked for advice because of chlorhexidine sensitization. Up to 2% chlorhexidine was found in 153 (1.9%) cosmetic products, which included creams, facial liquids, dental products, make-up removers, hair cosmetics, and, especially, eye care products.

Sources of sensitization

The sensitization to chlorhexidine in 25/36 cases resulted from Sibicort® and Duocort®, which also contain topical steroids. Current dermatitis in patient 10 began at a surgical site that had been cleansed with a chlorhexidine-containing surgical wash. Chlorhexidine-containing mouth washes appeared to have caused

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Table 1. Patients with positive patch test reactions to chlorhexidine during 1999–2009

Patient no., PT	Age (years)/sex	Diagnosis	Source of exposure	Localization	Concurrent patch test reactions	Exposure
1, ++	39/F	ACD	Sibicort, cosmetics	Face, extremities	2-Hydroxyethyl methacrylate, quaternium-5	Earlier and current
2, ++	75/F	Nummular, ACD	Chlorhexidine-containing hand scrub	Hands	Perfume mixture, propolis	Earlier
3, +	48/M	Nummular	Duocort	Leg	Budesonide, hydrocortisone 17-butyrate	Earlier and current
4, +	42/F	ACD	Sibicort, chlorhexidine-containing hand scrub	Hands	Thiuram mix	Earlier and current
5, +	84/F	ACD	Sibicort, cosmetics	Generalized	*p*-Phenylenediamine, dexpanthenol	Earlier
6, +	52/M	Atopic, ACD	Sibicort, cosmetics	Generalized	MCI/MI, MI	Earlier
7, ++	70/M	ACD	Chlorhexidine-containing hand scrub	Hand	*Myroxylon pereirae*, perfume mix I	Earlier
8, +	51/M	Atopic, ACD	Sibicort, cosmetics	Extremities, body	Ni, MCI/MI, MI	Earlier
9, +	52/F	ACD	Mouth wash, cosmetics	Scalp	*p*-Phenylenediamine	Earlier
10, +	13/M	Atopic, **ACD**	Duocort, surgical cleaner	Excision site	—	**Earlier and current**
11, +	56/F	ACD	Sibicort, cosmetics	Hands, arms	Tea tree oil, DMDM hydantoin, *Myroxylon pereirae*, MI	Earlier and current
12, +	24/M	ACD	—	Hands	Compositae mix	—
13, +	79/F	Nummular, ACD	Sibicort	Flexures, general	*Myroxylon pereirae*, tixocortol	Earlier and current
14, +	57/M	ACD	Sibicort	Hands, feet, general	Perfume mix I, neomycin, clioquinol	Earlier and current
15, +	32/M	ACD	Sibicort	Hands	Black rubber mix, *p*-phenylenediamine, quaternium-5	Earlier
16, +	61/M	Atopic, ACD	Duocort, Sibicort	Hands	Colophonium, perfume mix I	Earlier and current
17, +	67/M	Nummular	—	Face, body	MDBGN, perfume mix I	—
18, +	65/F	**Stomatitis**	Mouth wash	Mouth	MCI/MI, DMDM hydantoin	**Earlier and current**
19, +	60/M	Nummular, ACD	Sibicort, cosmetics	Hands	*Myroxylon pereirae*, imidazolidinyl urea*, MCI/MI, MI	Earlier and current
20, +	45/M	Nummular, stasis	Sibicort	Legs, arms	—	Earlier and current
21, +	19/F	Atopic, **ACD**	Duocort	Legs, body, head	—	**Earlier and current**
22, +	80/M	Stasis, **ACD**	Duocort	Legs, body	—	**Earlier and current**
23, ++	22/F	Atopic, ACD	Sibicort	Face, body, extremities	*p*-Phenylenediamine, black rubber mix	Earlier and current
24, +	74/F	Stasis	Sibicort	Leg, body	Lanolin, neomycin, thiuram mix, tixocortol, clioquinol*, *Myroxylon pereirae*	Earlier
25, +	80/F	Stasis	Sibicort	Leg, body	Nickel sulfate, cobalt chloride	Earlier
26, +	65/F	Stomatitis	Mouth wash	Mouth	Perfume mix I, *Myroxylon pereirae*	Earlier
27, +	68/M	Stasis	—	Leg	Lanolin, neomycin, tixocortol	—
28, +	77/F	ACD	Sibicort	General	Nickel sulfate, colophonium, perfume mix II, bacitracin	Earlier
29, +	44/F	ACD	Chlorhexidine-containing hand scrub	Hands	Nickel sulfate, cobalt chloride, *Myroxylon pereirae*, MCI/MI, MI	Earlier
30, +	63/F	Ulcer, ACD	Sibicort	Leg	Nickel sulfate, cobalt chloride, colophonium, thiuram mix	Earlier

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Table 1. *Continued*

Patient no., PT	Age (years)/sex	Diagnosis	Source of exposure	Localization	Concurrent patch test reactions	Exposure
31, +	56/F	Atopic, ACD	Sibicort, Duocort	Hands	*Myroxylon pereirae*, MCI/MI, MI, compositae mix	Earlier
32, +	39/F	Atopic	Sibicort	Flexures, face	Budesonide, DMDM hydantoin	Earlier
33, +	18/F	Atopic	Sibicort	Face	—	Earlier
34, +	63/M	ACD	Sibicort, Duocort	Hands	Nickel sulfate, cobalt chloride, perfume mix I, *Myroxylon pereirae*, bacitracin	Earlier and current
35, +	49/M	Seb, **ACD**	Sibicort, Duocort	Generalized	—	**Earlier and current**
36, +	58/M	ACD	—	Legs	Nickel sulfate, cobalt chloride, colophonium, thiourea mix	—

ACD, allergic contact dermatitis; Duocort; Duocort®, a cream with chlorhexidine digluconate 10 mg/g and hydrocortisone 17-butyrate 1.0 mg/g; nummular, chronic nummular dermatitis; atopic, atopic dermatitis; MCI, methylchloroisothiazolinone; MDBGN, methyldibromo glutaronitrile; MI, methylisothiazolinone; PT, strength of the patch test reactions; Sibicort, Sibicort®, a cream with 10 mg/g chlorhexidine digluconate and 10 mg/g hydrocortisone; stasis, stasis dermatitis; seb, seborrhoeic dermatitis; tixocortol, tixocortol 21-pivalate; ulcer, post-traumatic ulcer.

Exposure indicates either earlier or earlier and current exposure. Bold text indicates the cases with chlorhexidine as the major causative agent. 'Cosmetics' indicates suspected sources of exposure.

*[Correction added on 8 March 2011, after first online publication: imidazodinyl urea was changed to imidazolidinyl urea and kinolin was changed to clioquinol].

sensitization in 3 patients, 2 of whom had recently used these washes, and 1 who had used them some years previously. Four hand dermatitis patients had used chlorhexidine-containing skin disinfectants, but chlorhexidine avoidance alone did not reduce their symptoms.

Cosmetic products containing chlorhexidine were suspected of having caused worsening of skin symptoms in 7/36 patients.

Discussion

Chlorhexidine-containing topical medicines that are used to treat inflamed or injured skin were considered to be the principal sources of sensitization in this study. Although the over-the-counter hydrocortisone–chlorhexidine cream (Sibicort®) has been widely used for about 30 years in Finland, the prevalence of chlorhexidine-sensitized patients is rather low. Therefore, it seems that chlorhexidine is a weak contact sensitizer. In the sensitized patients, there was a history of chlorhexidine exposure in 32/36 cases, but chlorhexidine avoidance led only to partial or no recovery in a majority of cases; this finding is likely to be attributable to multiple other contributing factors.

A decreasing trend in the occurrence of chlorhexidine sensitization was reported in 1994 (7). In Finland, the sensitization rates were 1.5% in 1995 and 0.5% during 2001–2002, whereas 2.0% of patients had been sensitized to chlorhexidine in Switzerland in 1989 (7, 8). In line with these reports, the present results indicate that the frequency of chlorhexidine sensitization among dermatitis patients (0.47%) has at least not increased during the past decade.

In this study, evident allergic contact dermatitis or stomatitis caused by chlorhexidine was diagnosed in 5 patients. In the United Kingdom during the period from 1982 to 2002, allergic contact dermatitis caused by chlorhexidine was reported in 5 patients – mainly resulting from washing solutions (9). In our study, 1 patient developed allergic dermatitis from a surgical washing solution. Hand disinfectants were the principal source of chlorhexidine sensitization in 4 hand dermatitis patients, but multiple other factors also contributed; allergy to chlorhexidine probably contributed to the severity and duration of the hand dermatitis in these patients, but chlorhexidine avoidance did not lead to recovery. Chlorhexidine-containing hand scrubs were rather common at the end of the 1990s, but thereafter, and during the last 5 years of our study period, chlorhexidine for

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hand disinfection was increasingly replaced with alcohol solutions (12, 13). However, chlorhexidine is still useful, because of its broad antiseptic spectrum in minor surgical procedures (14).

Although our study population included mainly adult patients, sensitization to chlorhexidine was seen in 1 child and in 2 young adults with atopic dermatitis. Chlorhexidine sensitization may, however, be more frequent among children with atopic dermatitis, as they are seldom patch tested, and their atopic dermatitis is commonly treated with Sibicort® or Duocort® corticosteroid creams. Accordingly, chlorhexidine was reported to be one of the most common sensitizers among French children with atopic dermatitis (10). Underdiagnosed patient groups with potential contact sensitization may also occur among those sensitized as a result of anogenital treatments. A patient with balanitis caused by chlorhexidine washes was recently reported (15). Diagnosis among sensitized children and among patients sensitized by the use of intimate hygiene products may be missed, as these individuals tend to give up therapies that are either ineffective or worsen their symptoms.

It remains unresolved whether our stomatitis patients could have been previously sensitized via cutaneous exposure. As chlorhexidine is commonly used in mouth washes, the question of possible chlorhexidine-induced mucosal tolerance may be raised, as is seen for other allergens with mucosal exposure (16, 17). The sustained-release products used in certain dental applications release small amounts of chlorhexidine over prolonged periods (18). These products might favour the development of orally induced tolerance. Such tolerance induction may be common, as only occasional cases of allergic stomatitis caused by chlorhexidine have been reported. There are allergens that do cause sensitization via the oral route under certain circumstances (19, 20). Occasional oral contact sensitization to chlorhexidine cannot be excluded.

Chlorhexidine-induced symptoms may appear immediately after mucosal contact. None of our patients in the present cohort had experienced chlorhexidine-induced immediate-type symptoms. Prick tests with chlorhexidine gave negative results among those patients who were tested. Thus, we did not see any concurrent delayed and immediate-type sensitization, as is occasionally described (21). However, during our 10-year study period, we have seen 11 patients who were diagnosed as having IgE-mediated chlorhexidine allergy.

Multiple contact sensitivities were seen in 30/36 patients, most typically to common sensitizers in cosmetics such as perfumes and preservatives. Positive patch test reactions to *p*-phenylenediamine and chlorhexidine were seen in 4 adult patients. Similar results were obtained in a recent study, in which a 4-year-old boy was shown to have contact allergy to chlorhexidine and para-amino compounds (22). Concurrent reactivity to multiple contact allergens might reflect increased individual susceptibility to the development of contact sensitization, or indicate extensive exposure to multiple sensitizing chemicals, or both. Also, the possibility of 'angry back'or irritant reactions has to be considered in some cases, as skin irritation to chlorhexidine is possible, and testing with a dilution series was not carried out in this study. Some of the 1+ reactions to chlorhexidine may have been non-specific irritant reactions. Further testing with 0.25% and 0.125% chlorhexidine solutions might be helpful. The conventional use test or repeated open application test (23, 24) can also be used to evaluate chlorhexidine reactions. In creams containing corticosteroids and chlorhexidine, the steroid component may initially prevent clinical symptoms related to chlorhexidine allergy.

As chlorhexidine is found in some cosmetics, this source of exposure should be considered if the use of such products appears to cause dermatitis or delay improvement.

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