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ECZEMATOUS CONTACT ALLERGY TO CHLORHEXIDINE

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Abstract. A case is described of contact dermatitis resulting from the antiseptic chlorhexidine. Allergic nature of the reaction was proved by epicutaneous and intracutaneous testing, using different salts and solvents. False negative patch tests were obtained when chlorhexidine was applied in petrolatum, since chlorhexidine for physicochemical reasons is biologically and allergologically active in aqueous solutions only. Surfactants incorporated in emulsions may also interfere with the patch test response.

The properties of an antiseptic for common use should of necessity include a low toxicity in effective concentrations and the least possible sensitizing capacity. The frequency of eczematous contact allergy to quaternary ammonium bases is conveniently low, and, with the exception of a few cases of photoallergy, the same holds true for hexachlorophene. Chlorhexidine has won a similar reputation as an effective and non-toxic germicide, and there have been no published reports of sensitization to the compound.

Chlorhexidine is 1,1′-Hexamethylenebis [5-(*p*-chlorophenylbiguanide] (Fig. 1). Preparations for medical use include the digluconate cream and emulsion, the acetate and diacetate water solution and spirited water solution.

In the present case, a patient was primarily sensitized to the 1% digluconate emulsion.

CASE REPORT

The patient, a previously healthy woman aged 78, was admitted to the dermatologic ward of Malmö General Hospital in October 1970 because of a bullous erysipelas of her left lower leg. She was treated with intramuscular penicillin and was able to leave hospital 4 weeks later with a small, healing ulceration on her leg. She was then prescribed Hibitane® emulsion (ICI, U.K.) for topical treatment. There were also signs of a dispenser dermatitis, and a routine patch test with 20 standard allergens revealed positive reactions to nickel sulphate and paraphenylenediamine.

The patient returned 3 months later with an acute dermatitis starting on her left lower leg and thigh, extending to the face, especially the left cheek where the skin was oozing, and the eyelids. She denied the use of any topical preparation other than Hibitane®.

METHODS

Test solvents and concentrations are listed in Table I. Patch testing was performed with A1-test units (IMECO, Astra Agency Co., Sweden) and Leucoflex adhesive plaster (Beiersdorf, West Germany). The test substances were applied on the back for 48 hours and the tests read after a further 24 hours. Test sites showing erythema *and* infiltration or papules/vesicles were classed as positive. At intracutaneous testing, 0.1 ml of the test solution was administered and the test read after 48 hours; erythematous infiltration exceeding 5 mm was considered positive. Open tests were performed on the inside of the lower arms and read repeatedly between 24 and 72 hours. Gas chromatographic analysis (Varian aerograph 1400, with a 3% OV 17 column) was performed on alcoholic and aqueous solutions of chlorhexidine diacetate, freshly prepared as well as 3 months old, and of *p*-chloroaniline.

RESULTS

Patch tests with Hibitane® emulsion (chlorhexidine digluconate) were strongly positive with a papulo-vesicular response (Table I). Tests with chlorhexidine diacetate solutions in water and in ethanol also gave positive reactions while open tests were negative. Patch tests with chlorhexidine diacetate in petrolatum were negative, even in high concentration. Control testing of 24 patients with various dermatoses with 0.5% diacetate ethanol solution gave negative results. Intracutaneous testing with chlorhexidine diacetate was positive in the patient, negative in ten controls.

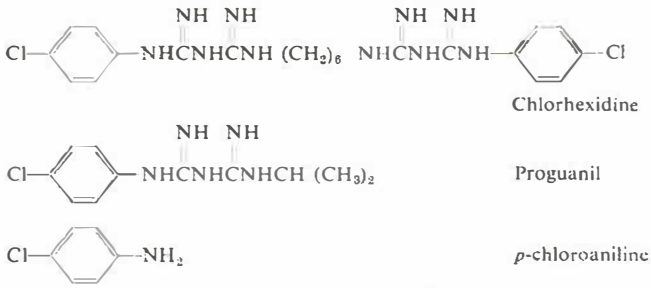

Fig. 1. Structural formula of chlorhexidine and two related compounds.

When the patient was retested 4 months later the findings were principally the same but the reactions much weaker. She was then also tested with two breakdown products of chlorhexidine: proguanil which is half the molecule of the mother compound, and *p*-chloroaniline (Fig. 1); these tests were negative.

Table I. *Test reactions with different salts and derivatives of chlorhexidine (CH)*

Compound Solvent	Conc. (%)	First testing	Second testing
Patch tests			
CH digluconate (Hibitane®)			
Emulsion[a]	1.0	+	+
CH diacetate			
Ethanol	0.5	+	
Water	0.05	+	−
Petrolatum	0.1	−	
Petrolatum	1.0	−	
Emulsion o/w[b]	0.05		−
Emulsion o/w[b]	1.0		+
Emulsion w/o[c]	0.05		−
Emulsion w/o[c]	1.0		+
p-chloroaniline			
Ethanol	1.0		−
Petrolatum	1.0		−
Proguanil			
Ethanol	1.0		−
Petrolatum	1.0		−
Open tests			
CH diacetate			
Ethanol	0.5	−	
Water	0.05	−	
Intracutaneous tests			
CH diacetate			
Saline, isotonic (pH 7.9)	0.005		+

[a] Contains liquid paraffin, white petrolatum, cetostearol, cetyl & stearylmacrogolether, and water.
[b] Contains cetanol, adeps lanae, polysorbate 80, methagin, propagin, and water.
[c] Contains white petrolatum, Span 80, methagin, propagin, and water.

Gas chromatography showed only one peak in the chlorhexidine diacetate solutions which was different from that of *p*-chloroaniline.

DISCUSSION

The allergic nature of the positive patch tests in our patient to the chlorhexidine preparations seems to be established. Firstly, the patient had used the emulsion on the excematous skin of a hypostatic leg which furnishes the optimal sensitization milieu (6). Secondly, the test showed a papulo-vesicular response to a low concentration of the chemical, both as different salts and in different solvents; patch tests in controls were negative. Thirdly, the patient also showed positive reactions at intracutaneous testing; such correlation occurs regularly in eczematous contact allergy (2) although it may also be observed in a situation where an allergic pathogenesis is in question (4).

In aqueous solutions of chlorhexidine a slow hydrolysis may result in the formation of small amounts of *p*-chloroaniline (3). It was shown by gas chromatography, however, that *p*-chloroaniline was not present in old or fresh solutions and the patch test with this substance was negative.

Although chlorhexidine is widely used as an antiseptic, contact allergy appears to be extremely rare. We know of two cases of true hypersensitivity, one having occurred in England (1), and one in Sweden (9). A third case turned out to be due to a perfume constituent of the preparation (7). With the extensive use of chlorhexidine it is surprising that more cases have not been registered; we would like to propose one possible explanation for this.

Chlorhexidine is essentially insoluble in hydrocarbon solvents (5) which excludes their use for

epicutaneous testing with this substance. It is of interest that in our patient patch tests with chlorhexidine in water and alcohol were positive though negative when using the routine solvent, petrolatum, even in high concentrations. On the other hand, when the compound was incorporated in an oil-in-water or a water-in-oil emulsion it gave positive patch tests. It is thus possible that chlorhexidine is not yielded by the mineral lipid for penetration to the skin in proper amounts. Early studies have shown this principle to imply several compounds (8). Testing chlorhexidine with petrolatum as the only vehicle might consequently give false negative results.

It has been shown that chlorhexidine in solution is inactivated by increasing concentrations of polysorbate 80 (5). This may explain why the patch test was negative to a low concentration of chlorhexidine using the oil-in-water emulsion (containing 2.5% polysorbate 80). It is possible that the surfactant Span 80, included to 2.5% in the water-in-oil emulsion, plays a similar interactive role. Obviously, chlorhexidine is active only in the aqueous phase of emulsions.

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