

Is there a risk of sensitization and allergy to chlorhexidine in health care workers?

L. H. GARVEY¹, J. ROED-PETERSEN² and B. HUSUM¹

Danish Anaesthesia Allergy Center, Departments of ¹Anaesthesiology and ²Dermatology, Gentofte University Hospital, Copenhagen, Denmark

Background: In Denmark, chlorhexidine is the standard disinfectant in most hospitals and health care workers are repeatedly exposed to it. The aim of this study was to establish whether there is a risk of sensitization and allergy to chlorhexidine from this type of exposure.

Methods: Two hundred and forty-eight doctors, nurses and auxiliary staff were invited to participate in the study. One hundred and four individuals took part in the full study including skin tests and a questionnaire and a further 74 individuals filled in the questionnaire giving a total of 178 questionnaires (72%). Patch tests with chlorhexidine gluconate 1% and chlorhexidine acetate 1% were performed looking for type IV (delayed type) allergy. A prick test with chlorhexidine gluconate 0.5% and an intradermal test with chlorhexidine 0.0002% were performed looking for type I (immediate type) allergy.

Results: There were *no* positive tests in any of the 104 individuals tested (99% confidence interval 0–4.9%). There was a predominance of females in both groups and the overall median age was 42 years

(28–63). No one in the group not tested reported to have a verified or suspected allergy to chlorhexidine.

Conclusion: In this first study to examine the risk of type I and type IV allergy to chlorhexidine in health care workers with daily exposure to chlorhexidine, we did not identify allergies to chlorhexidine in any of the 104 individuals tested or in the additional 74 individuals who completed the questionnaire. We conclude that an allergy to chlorhexidine in health care workers is likely to be rare.

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ALLERGIC reactions to chlorhexidine in patients have been reported in recent years from all over the world. Reported reactions range from mild rashes to profound anaphylactic shock and in most cases the patients had a history of mild reactions on previous exposure to chlorhexidine. In the Danish Anaesthesia Allergy Centre, we investigate patients with allergic reactions during anaesthesia (1) and during the past 3 years we have identified seven cases of anaphylactic reactions to chlorhexidine, four of which have been published (2).

In the present study, we set out to establish whether health care workers with daily exposure to chlorhexidine could be at risk of sensitization and allergy to it. We feel it is an important question to answer, as the results could have implications on work routines and hygiene precautions.

Methods

The local Human Ethics Research Committee approved the study protocol. Letters were sent to

248 members of staff at Gentofte University Hospital (all anaesthesiologists, anaesthetic nurses, intensive care nurses and auxiliary nurses in the Department of Anaesthesiology and all operating department nurses in the Department of General Surgery) inviting them to participate in the study. It was planned to undertake the study over a 4-week period during normal working hours. The study comprised skin testing with chlorhexidine and a questionnaire. Individuals needed to be tested on two separate days and they were given a choice of eight sets of dates in which to participate. Criteria for exclusion from skin testing were pregnancy or breast-feeding and treatment with antihistamines in the days proceeding skin testing. A second invitation to participate was sent to initial non-responders and eventually a third letter with the questionnaire was sent to non-responders and individuals who had declined to take part in the skin testing. In all three letters, individuals were urged to make themselves known to the organizers if they had a verified allergy or strongly suspected an allergy to chlorhexidine.

Test procedure

Patch tests using Finn Chambers[®] (Epitest Ltd, Oy, Finland) and Scanpore tape[®] (Alpharma A/S, Oslo, Norway) were applied to the participants' back. Solutions used were chlorhexidine digluconate 1% and chlorhexidine acetate 1% (both in water). They were removed 48 h later by the participant, who was instructed to contact the Dermatology Laboratory in case of itching or local irritation. Patch tests were all inspected by the same person 72 h after application, and if there were signs of reaction or irritation they were read by a dermatology nurse with many years experience in patch testing. A prick test with chlorhexidine gluconate 0.5% and an intradermal test with chlorhexidine gluconate 0.0002% were performed on the forearm with a normal saline negative control and a histamine positive control. The same specially trained nurse performed all prick- and intradermal tests. Each test was observed for 15 min and participants filled in the questionnaire in the waiting time. The questionnaire included demographic data on sex, age and profession. Detailed questions on allergic symptoms in the workplace and outside, known allergies (defined as allergies previously verified on skin testing) and familial disposition to allergic diseases were asked, to determine the extent of allergic disease in this population. Questions about known exposure to chlorhexidine outside the workplace and length of exposure to chlorhexidine in the workplace (determined as years in current profession) and number of previous operations were asked to estimate the total exposure to chlorhexidine.

Patch tests were read in accordance with the International Contact Dermatitis Research Group guidelines and irritative reactions were considered negative. The criterion for a positive prick test was development of a wheal larger than half the diameter of the wheal of the positive control. The criterion for a positive intradermal test was doubling of the diameter of the wheal induced.

Exposure to chlorhexidine

Chlorhexidine is used as the standard skin disinfectant in Gentofte University Hospital for both patients and health care workers. In the Operating Department, chlorhexidine 0.5% in ethanol 70% is used for hand disinfection for nurses and surgeons scrubbing prior to performing surgery. Chlorhexidine 0.5% in ethanol is also used prior to all invasive procedures including venous and arterial cannulation, which are often performed by staff without gloves thus exposing them to chlorhexidine on their hands. Finally,

chlorhexidine 0.5% with or without glycerol is the standard hand disinfectant used all over the hospital including the Intensive Care Unit for hand disinfection between patient contacts. All groups of participants in our study are thus in daily contact with chlorhexidine in the workplace. To try and establish the total exposure to chlorhexidine, the number of years in the current profession was established, as was known exposure to chlorhexidine in the home or in connection with previous surgery.

Results

One hundred and four (42%) individuals volunteered to take part in the full study including skin tests and filling in the questionnaire (group I). A further 74 (30%) declined to take part in skin testing but filled in the questionnaire (group II), giving a response rate of 72% on returning the questionnaire. The sex and occupation of the study population can be seen in Table 1. Reasons for declining skin testing were needle phobia and not being able to fit testing in around changing shifts.

None of the 104 participants tested positive to chlorhexidine (99% confidence interval 0–4.9%). Nine participants had an irritative response to either or both of the patch tests, but this is well known and these responses are generally considered negative. There were no positive prick- or intradermal tests either. One participant had taken antihistamines causing the positive control to be negative. After 3 days without antihistamines, she still tested negative when her response to the positive control had normalized.

The results of the questionnaires can be seen in Table 2. The median age in the group who were skin tested (group I) was 42 years (29–63) and this group had a median of 18 years (2–43) in the medical

Table 1

Study population ($n = 178$) divided into test groups, sex and occupation.

Occupation	Group I Skin testing and questionnaire $n = 104$	Group II Questionnaire only $n = 74$
Doctors	26 (21 m, 5 f)	7 (4 m, 3 f)
OD nurses	22 (0 m, 22 f)	12 (0 m, 12 f)
Nurse anaesthetists	32 (2 m, 30 f)	17 (2 m, 15 f)
ICU nurses	17 (0 m, 17 f)	33 (2 m, 31 f)
Auxiliary nurses	7 (1 m, 6 f)	5 (0 m, 5 f)
Total	104 (24 m, 80 f)	74 (8 m, 66 f)

m: males; f: females.

Table 2

Data from questionnaires. Data are median (range) or number of persons (%).

	Group I Skin testing and questionnaire <i>n</i> = 104	Group II Questionnaire only <i>n</i> = 74
Demographic data		
Males	24 (23.1%)	8 (10.8%)
Females	80 (76.9%)	66 (89.2%)
Age (years)	41 (28–62)	42 (29–63)
Exposure to chlorhexidine		
Time in medical profession (years)	18 (2–43)	15 (3–40)
Chlorhexidine use at home	33 (31.7%)	14 (18.9%)
Previous surgery	1 (0–8)	1 (0–6)
Allergic symptoms experienced		
At home	66 (63.5%)	39 (53.0%)
In the workplace	50 (48.0%)	34 (46.0%)
During admission to hospital	3 (2.9%)	4 (5.4%)
On visits to the dentist	0	0
On visits to the GP	0	0
Verified allergies	35 (33.7%)	25 (33.8%)

profession. The median age in the group who was not skin tested (group II) was 41 years (28–62) with a median of 15 years (3–40) in the medical profession. There were more females in both groups with 80 out of 104 (76.9%) in group I and 66 out of 74 (89.2%) in group II. In group I, 50 (48%) individuals reported having, or having had, one or more allergic symptoms during working hours, while 66 (63.5%) reported having or having had one or more allergic symptoms in the home. The corresponding figures in group II were 34 (46%) with symptoms at work and 39 (53%) with symptoms at home. Regarding exposure to chlorhexidine, individuals in group I had a median of 1 operation (0–8) and 33 (31.7%) used chlorhexidine in the home. In group II, individuals had a median of 1 operation (0–6) and 14 (18.9%) used chlorhexidine in the home. Three individuals in group I and four in group II had encountered allergic symptoms in connection with admission to hospital. These reactions were localized rashes after plaster, elastic underwear and administration of morphine and systemic rashes after administration of penicillin, i.v. urography and surgery.

Thirty-five (33.7%) individuals in group I and 25 (33.8%) in group II had known allergies verified on previous skin testing. Of these, 15 (14.4%) in group I and 10 (13.5%) in group II had a verified allergy to more than one of the following: pollen, fur animals, dustmites, vegetables/fruit and were defined as atopic individuals. Eleven (10.5%) in group I and five (6.7%) in group II had an nickel allergy and this was the most prevalent allergen. One individual in group I and two in group II had a verified latex

allergy, and two in group I and one in group II had a verified allergy to formaldehyde.

Discussion

We believe this is the first study looking at the incidence of both type I and type IV allergies to chlorhexidine in health care workers with daily exposure to it. In most Danish hospitals, chlorhexidine is widely used by health care workers in all specialties for hand disinfection between patient contacts, in operating theatres for scrubbing prior to performing/assisting surgical procedures and by staff disinfecting patients' skin prior to performing invasive procedures including venous cannulation or arterial puncture, which are often performed ungloved.

We investigated a population of anaesthesiologists, anaesthetic nurses, intensive care nurses and operating department nurses who all had daily exposure to chlorhexidine on their hands.

All 104 individuals tested negative for chlorhexidine, both on patch tests, which determine type IV (delayed type allergy) and on prick- and intradermal tests, which determine a type I (immediate type allergy). We cannot rule out that some of the individuals not tested have an allergy to chlorhexidine, but all individuals not participating were requested in three separate letters to come forward if they had a verified allergy to chlorhexidine or strongly suspected it. No one came forward.

Serious anaphylactic reactions to chlorhexidine in patients have been reported recently in connection with central venous cannulation (3–6), passing of

urethral catheters (7, 8) and in connection with surgery and anaesthesia (2, 9). In addition, earlier reports have been of reactions in connection with topical use of chlorhexidine on wounds (10–12) and intact skin (13, 14), on oral mucosa in connection with dental treatment (15) and a variety of other applications. Interestingly, there is a predominance of reports concerning male patients, often over the age of 50 years, and this is also reflected in the four cases previously published from the Danish Anaesthesia Allergy Centre (2). These findings are supported by a couple of studies of contact dermatitis to chlorhexidine published in the dermatological literature (16, 17).

The population of health care workers investigated in our study was predominantly female with a median age of 42 year and studies of contact dermatitis (type IV allergy) to occupational allergens including chlorhexidine in similar study populations found a very low incidence (18, 19).

Other studies on contact dermatitis to occupational allergens have shown an incidence of type IV allergy to chlorhexidine gluconate of 1–2.5% in dermatology patients (20–24) and health care workers (25), and an increased incidence in patients with leg ulcers who had used wound dressings containing chlorhexidine (21–23).

One study showed that hand dermatitis to chlorhexidine hand disinfectant in surgeons was more prevalent at high (4%) concentrations, but that allergy could not be proven in all cases, suggesting an irritant reaction (26).

The question is whether sensitization and allergy can occur from application of chlorhexidine to intact skin. Some early studies have shown that small amounts of chlorhexidine can be absorbed through intact skin, but that this is much more likely in preterm babies than in adults or term babies (27, 28). Health care workers mainly have contact with chlorhexidine on intact skin and the risk of sensitization in this way may be limited, although many have dry and chapped skin, especially in the winter months.

It may be that sensitization to chlorhexidine is more likely after application to mucous membranes in the urethra or mouth, or when chlorhexidine enters the bloodstream directly, in connection with central venous cannulation or as coating on the central line itself. This theory may be indirectly supported by a small study of the incidence of IgE and IgG antibodies against chlorhexidine in Japanese and British patients and nurses. IgE antibodies against chlorhexidine were found in Japanese patients who had experienced anaphylactic reactions on exposure to

chlorhexidine during surgery and anaesthesia. None of nurses (neither Japanese nor British) investigated had IgE antibodies against chlorhexidine despite daily exposure to chlorhexidine on their hands (29).

The mode of sensitization to chlorhexidine is thus not clear, and interestingly some patients have been reported to have a combined type I and type IV allergy (2, 30–32). The significance of a combined allergy is unknown, and the question is whether the two types of allergy occur simultaneously, or if not, which appears first. In many of the cases, one or more mild reactions preceded the anaphylactic shock (2, 9) and in most cases these reactions can be traced back to previous known chlorhexidine usage. Chlorhexidine is an ingredient in a large number of preparations available over the counter such as creams, lotions, lozenges, mouthwash, etc. and sensitization could possibly have occurred using some of these preparations.

Some of our study population was also exposed to chlorhexidine in the home and most individuals had had at least one operation exposing them to chlorhexidine before surgical incision, on venous cannulation, etc. For sensitization and allergic reactions to occur, however, it may be that exposure needs to be either (a) repeated within a short time, (b) more prolonged as in lubricant jelly left in the urethra after urinary catheterization or (c) more intense as in exposure directly into a vein during central venous cannulation or surgical incision.

We did not identify chlorhexidine allergy in any of 104 health care workers skin tested in our study. We realize that with a relatively small study like this we cannot rule out an incidence of allergy to chlorhexidine even at the percent level. We still believe, however, that although there is a risk of sensitization and allergy to chlorhexidine in health care workers it is likely to be small, but that larger studies would have to be undertaken to confirm this. It is important to be aware of the risk and to test health care workers for allergies to chlorhexidine if relevant, but we do not believe it to be a problem of a magnitude that warrants changes in work routines and hygiene precautions.

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Address:
Lene Heise Garvey
Danish Anaesthesia Allergy Centre
Department of Anaesthesiology
Gentofte University Hospital
Niels Andersens Vej 65
DK-2900 Hellerup
Denmark
e-mail: daac@gentoftehosk.kbhamt.dk