NEW HORIZONS
– ALLERGY –

NUMBER 2, 2006

Anaphylaxis to chlorhexidine

Summary

In many countries, the disinfectant chlorhexidine is widely used both in healthcare and in the home, and exposure to it is almost inevitable. It has few side effects when used on skin or mucous membranes in low concentration. However, hypersensitivity reactions to chlorhexidine have been reported from around the world since the mid-1960s. These reactions range from mild skin reactions to profound anaphylactic shock with cardiac arrest. For the past seven years in Denmark, there has been a special focus on anaphylaxis to chlorhexidine in connection with anaesthesia. Testing with chlorhexidine has been part of the standard investigation programme at the Danish Anaesthesia Allergy Centre (DAAC) when investigating patients suspected of suffering anaphylactic reactions during anaesthesia. A relatively large number of patients investigated at the DAAC have tested positive to chlorhexidine in skin testing, and most of them have been shown to have IgE antibodies to chlorhexidine (ImmunoCAP™, Phadia AB, Sweden). Several clinical features of the reactions of patients with chlorhexidine allergy have been found to be similar to those of latex allergy. For example, both substances are used extensively during surgery and anaesthesia, reactions occur 20 to 40 minutes after exposure, and latex and chlorhexidine are rarely suspected when anaphylaxis does occur.

Despite the wide application of chlorhexidine as a skin disinfectant for healthcare workers, it has not been proven to cause sensitisation in this population.

Allergy to chlorhexidine has been shown to be IgE-mediated and diagnosis is made on the basis of a combination of clinical history, skin testing and measurement of IgE antibodies to chlorhexidine. Future challenges in this field will be to further refine the diagnostic tests, to carry out studies on the mode of sensitisation, and to try to define high-risk populations in an attempt to prevent these rare but serious reactions.

Lene Heise Garvey, MD

Danish Anaesthesia Allergy Centre,
Department of Anaesthesia, HOC 4231,
Copenhagen University Hospital,
Rigshospitalet,
Denmark

Introduction

Chlorhexidine digluconate is a cationic bis-biguanide disinfectant (**Fig. 1**) with broad-spectrum anti-microbial activity and low toxicity when used externally in mammals. It has a wide variety of uses, including skin disinfection prior to surgery and invasive procedures ranging from simple blood tests to major operations. It is used to disinfect the hands of healthcare workers between patient contacts and before sterile procedures, and is commonly used in connection with and after dental procedures. In addition, it is an ingredient in exploration gel used for vaginal and rectal examinations and in urethral gel used before inserting catheters. Outside of healthcare, it is found in simple, over-the-counter products for disinfecting minor wounds and scratches in the home. It is also an ingredient in a large number of home care and personal hygiene products such as cleaning fluids, toothpastes, mouth rinses, plasters and dressings, ointments and suppositories. Chlorhexidine diacetate has been used in some countries as a commercial disinfectant in connection with food handling (USA Environmental Protection Agency, 1996), disinfection of udders before milking livestock, and veterinary disinfection. It has also been used as a preservative in products as diverse as lozenges, antacid preparations and contact lens cleaning fluids.

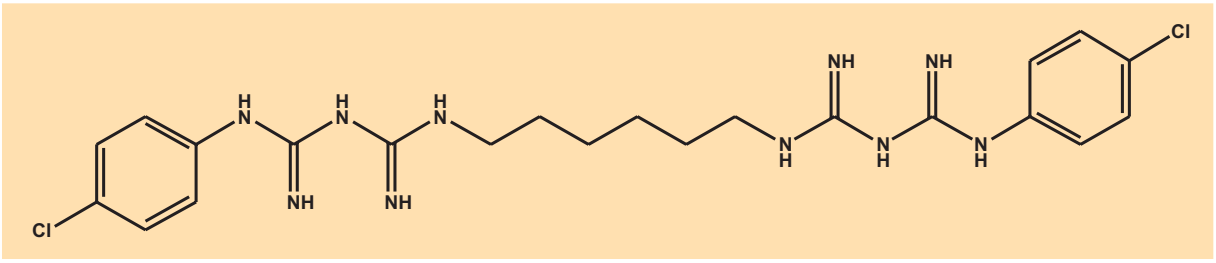

Figure 1. Chlorhexidine.

It is thus evident that a large proportion of the population will come into contact with chlorhexidine with varying degrees of exposure. In a multinational study of atopic individuals, a prevalence of IgE antibodies to chlorhexidine in the order of 2% was found (Personal communication, Erik Florvaag, Haukeland University Hospital, Bergen, Norway) .

The rest of this article will focus mainly on the use of chlorhexidine digluconate in healthcare. The term chlorhexidine will be used synonymously with chlorhexidine digluconate.

History of anaphylaxis to chlorhexidine

The clinical usefulness of chlorhexidine was first described in 1954 (1). In 1965, the first report of skin hypersensitivity appeared in The Lancet (2), but the problem was concluded to be rare when taking into account the substance's widespread use (3). In the early 1980s, reports from Denmark described contact dermatitis caused by chlorhexidine in patients with skin disorders, and an increased incidence was seen in patients who had used chlorhexidine for disinfecting chronic leg ulcers (4;5). At the same time, a report appeared from Japan of a severe anaphylactic reaction to chlorhexidine used in an anaesthetised patient (6). In the period 1967-1984, nine reports of anaphylactic shock related to the use of chlorhexidine on mucous membranes were collected in Japan, which led to an official recommendation to avoid using the substance on mucous membranes. It was also recommended to use the lowest bactericidal concentration (0.05%) for contact with broken skin barrier (7).

Sporadic case reports from all over the world have since followed. These concern severe anaphylaxis to chlorhexidine from different modes of exposure during surgery and anaesthesia, e.g. urological procedures and urinary catheter insertion (8), other surgical procedures (9) and central venous line insertion (10).

Anaphylaxis to chlorhexidine during anaesthesia in Denmark

Anaphylactic reactions during anaesthesia have been investigated systematically in Denmark since the Danish Anaesthesia Allergy Centre (DAAC) was established in 1998. Patients from all over Denmark with suspected anaphylaxis during anaesthesia are investigated using a standardised programme of skin testing and *in vitro* testing (mast cell tryptase and IgE antibody testing using the Phadia ImmunoCAP™ system) (11). Patients are tested with all drugs and substances used during anaesthesia and surgery prior to the suspected anaphylactic reaction. The investigation programme was initially based on recommendations from other centres with many years experience in investigating anaphylaxis in anaesthesia (12;13). Testing for natural rubber latex was included as standard in all patients. Latex exposure is in general unavoidable during routine anaesthesia and surgery, and the established centres attributed 10 to 15% of all anaphylaxis cases to latex (12).

One of the first patients tested at the DAAC was an elderly man who had a recurring urological problem. He had had an anaphylactic shock during previous surgery, but needed a further procedure. The attending anaesthetist was careful to avoid all drugs used previously as well as exposure to latex, but the patient developed anaphylaxis despite these precautions. He was referred to the DAAC for investigation and it became clear that he must have reacted to something administered by the surgeon or operating assistants, since all drugs administered by the anaesthetist tested negative. He had been exposed to glycine soap, irrigation fluid and a lidocaine/chlorhexidine urethral gel. When all were tested, the skin prick test was positive for chlorhexidine digluconate.

Due to the widespread use of chlorhexidine during anaesthesia and surgery in Denmark, it was decided in 1999 to include testing for chlorhexidine as a standard in all patients investigated at the DAAC. The case of the elderly man and three similar cases that were diagnosed during subsequent years were published in 2001 (14). Some interesting common features were observed in all four. All patients were males aged >50 years and all had severe anaphylaxis in connection with anaesthesia and surgery/invasive procedures. One patient even had a cardiac arrest on two separate occasions. Reactions occurred 20 to 40 minutes into the operation and all patients had a history of previous milder reactions in connection with exposure to chlorhexidine.

At that time, it was suggested that allergy to chlorhexidine displayed several features that were comparable to those of latex allergy: 1) The allergen probably needs to pass through a broken skin or mucosa barrier for a reaction to occur. This accounts for the reactions occurring 20 to 40 minutes after initial exposure. 2) It causes mild non-specific reactions on some occasions, but has the potential to cause serious life-threatening anaphylaxis. 3) As chlorhexidine and latex are not drugs, they can be overlooked as the cause of anaphylaxis during anaesthesia. This leads to the risk of potentially dangerous re-exposure. 4) In some patients, a combined IgE and lymphocyte-mediated allergy has been noted.

It was recommended that investigations of patients with suspected anaphylaxis during anaesthesia and surgery should include testing for chlorhexidine, and that patients should be questioned about symptoms in connection with previous exposure to chlorhexidine (14).

During 1999-2005, when systematic testing with chlorhexidine was performed at the DAAC, a total of 12 patients tested positive for chlorhexidine on skin testing (data presented at the XXV Congress of the European Academy of Allergology and Clinical Immunology, June 2006). Considering that approx 450,000 anaesthetic procedures are carried out in Denmark each year, this suggests a very low incidence of anaphylaxis to chlorhexidine in this patient group, even if there is an element of underreporting. Although rare, it nevertheless remains a serious problem as three of the 12 patients had cardiac arrests in connection with the anaphylaxis.

Sensitisation to chlorhexidine in healthcare workers

With allergy to chlorhexidine established as a rare but serious problem in patients undergoing anaesthesia and surgery, the question of sensitisation of healthcare workers was raised at the DAAC. As mentioned previously, several aspects pointed towards some features common with latex allergy, which over the past three decades has proven to be a problem for healthcare workers due to their daily exposure (15). Chlorhexidine digluconate in combination with either alcohol or glycerol is the standard skin disinfectant used in most Danish Hospitals. Healthcare workers in Denmark are therefore exposed to chlorhexidine daily through hand disinfection between patient contacts or prior to performing surgery or invasive procedures. This widespread exposure was thus thought to be a potential risk factor for sensitisation against chlorhexidine. However, only a few studies concerning healthcare worker sensitisation to chlorhexidine were identified in the literature, and all concerned delayed, lymphocyte-mediated allergy (16-18).

A study was thus performed looking at the prevalence of sensitisation and allergy to chlorhexidine in healthcare workers in the Department of Surgery and Anaesthesia at a hospital in the Copenhagen area. 248 members of staff were invited to participate in the study, which comprised a questionnaire plus testing to determine IgE-mediated allergy (skin prick test with 0.5% chlorhexidine digluconate, intradermal test with 0.0002% chlorhexidine digluconate), and lymphocyte-mediated allergy (patch test with chlorhexidine digluconate and chlorhexidine acetate, both 1% in water).

A total of 104 individuals agreed to be tested and none were positive in any of the test modalities. The study raised questions about the mode of sensitisation to chlorhexidine. It was suggested that one of the reasons for not finding sensitised healthcare workers was that sensitisation was unlikely to occur through intact skin. This was supported by work done looking at the absorption of chlorhexidine from the skin in neonates, which concluded that small amounts of chlorhexidine can be absorbed through intact skin, but that this is more likely in preterm babies than in term babies or adults (19;20).

The conclusion of this study was that since the numbers were small, the results could not statistically rule out a significant prevalence of allergy to chlorhexidine in healthcare workers, even at the percent level, and that larger studies were needed. It was therefore recommended that awareness of the small risk of sensitisation to chlorhexidine in healthcare workers was important, but that no changes in work routines or hygiene precautions were warranted (21).

Mechanism and diagnosis

IgE antibodies to chlorhexidine

Clinically, an IgE-mediated mechanism is suspected due to the severe immediate hypersensitivity reactions seen in cases of chlorhexidine anaphylaxis. This suspicion is supported by 1) IgE antibody to chlorhexidine has previously been detected in serum of a small number of patients (22-24), and 2) skin testing (both prick and intradermal testing) has proved useful in the diagnosis of allergy to chlorhexidine (11;25). Recently, a new commercial assay (ImmunoCAP™, Phadia AB, Sweden) has become available. One small Belgian study of four patients with perioperative anaphylaxis showed a good correlation between positive skin prick test for chlorhexidine and the presence of IgE antibodies to chlorhexidine above the threshold of 0.35 kU_A/L. A control group of 30 patients had a negative prick test and no IgE antibody to chlorhexidine (26). At the DAAC, 11 of 12 patients with anaphylaxis in connection with anaesthesia and positive skin tests to chlorhexidine had IgE antibodies to chlorhexidine. Ten controls with a similar clinical presentation, but with negative skin tests to chlorhexidine, did not have IgE antibodies (data presented at the XXV Congress of the European Academy of Allergology and Clinical Immunology, June 2006). In addition, no IgE antibodies to chlorhexidine were found in the more than 80 patients with negative skin tests to chlorhexidine investigated at the DAAC since 2004 (Personal communication, Mogens Krøigaard, DAAC).

Recently, a group from the Skin and Allergy Hospital, Helsinki, Finland, has looked at patients with positive skin prick tests to chlorhexidine. A total of 1314 patients referred for allergy investigation were tested for chlorhexidine as part of routine prick testing. Case records of 33 patients with a positive prick test were retrieved and the patients were invited for further testing. Fourteen patients had a blood sample analysed for IgE antibodies against chlorhexidine, using an experimental prototype of chlorhexidine ImmunoCAP™, and six samples were positive. The yield in this population was therefore not as high as in the other two studies mentioned. In this study, sera were taken a long time after the adverse reaction, on average 29 months after the positive prick test, which might partly explain the results. It is recommended, that samples for Specific IgE antibodies tested for drugs should preferably be taken no later than 6 months after the reaction. In addition, chlorhexidine produced irritant reactions in a number of patients and this can cause some uncertainty about the positive nature of the skin reaction (27).

Skin testing

Skin testing comprises a variety of tests, but the most commonly used are skin prick tests and intradermal tests, both for diagnosing IgE-mediated allergy, and patch tests for diagnosing lymphocyte-mediated allergy. Chlorhexidine is largely atoxic when used for skin disinfection or in low concentrations on mucous membranes, but has severe irritant properties when used in higher concentrations. It is therefore very important to use the right dilution for skin testing to reduce the risk of false-positive reactions. A review of the literature on skin testing for chlorhexidine showed that a wide range of dilutions had been used. For prick testing, dilutions were in the range of 0.0005% to 4% and for intradermal testing 0.0002% to 0.05% (25).

Based on the experience of testing several hundred patients and staff, the dilutions used at the DAAC are 0.5% chlorhexidine digluconate for skin prick testing and 0.0002% chlorhexidine digluconate for intradermal testing (11;21). Skin testing in general requires experienced staff that can prepare dilutions and perform and read tests reliably. In clinics were these criteria are fulfilled, skin testing can be very useful and have a high sensitivity and specificity for many drugs. However, if the wrong dilutions or diagnostic criteria are used, testing becomes unreliable. Therefore skin testing should be carried out in specialist centres and, wherever possible, be supplemented with clinical information and relevant *in vitro* testing.

Other diagnostic tests

In patients with IgE-mediated allergy, the allergen can trigger both mast cells and basophils to release histamine and other mediators. This is utilised in basophil allergen threshold challenge tests such as the leukocyte histamine release test (28) or by flow cytometric analysis of *in vitro* activated basophils to measure the up-regulation of CD63 in the cell membrane (26;29).

As yet, there is not much experience with these tests in anaphylaxis to chlorhexidine and they are thus presently used as supplemental tests only.

Future prospects in anaphylaxis to chlorhexidine

Anaphylaxis to chlorhexidine is a rare but serious complication of the use of a substance that has proven to have excellent anti-microbial properties combined with a fairly benign safety profile.

The incidence of anaphylaxis to chlorhexidine is not known, but it is likely to be underestimated due to the fact that chlorhexidine is not a drug and is thus rarely suspected in connection with anaphylaxis. Data from the DAAC show that in Denmark, chlorhexidine causes 10 to 15% of positive reactions in patients investigated after suspected anaphylactic reactions during anaesthesia. This patient group is thus likely to represent a high-risk population. Data from centres in other countries investigating patients suspected of anaphylaxis in anaesthesia do not so far show the same tendency. However, no other centres test with chlorhexidine as part of the standard investigation programme, as is done at the DAAC.

Challenges for the future will be to further refine the *in vitro* tests that have so far shown promise as useful adjuncts to skin testing. In addition, studies should be carried out to look at the mode of sensitisation of chlorhexidine allergy and to try to further define high-risk groups for this rare allergy. In this way, it is hoped that hypersensitivity can be suspected early and a correct diagnosis confirmed, thereby protecting patients from repeated and potentially lethal anaphylactic reactions.

References

1. Davies GE, Francis J, Martin AR, Rose FL, Swain G.
1:6-Di-4'-chlorophenyldiguanidohexane (hibitane); laboratory investigation of a new antibacterial agent of high potency.
Br J Pharmacol Chemother 1954 Jun;9(2):192-6.
2. Birdwood B.
Reaction to Chlorhexidine and Cetrimide.
Lancet 1965 Mar 20;43:651-2.
3. Nickel KM, Marsden CW.
Reaction to chlorhexidine and cetrimide.
Lancet 1965 Apr 10;1(7389):821-2.
4. Osmundsen PE.
Contact dermatitis to chlorhexidine.
Contact Dermatitis 1982 Mar;8(2):81-3.
5. Lasthein AB, Brandrup F.
Contact dermatitis from chlorhexidine.
Contact Dermatitis 1985 Nov;13(5):307-9.
6. Cheung J, O'Leary JJ.
Allergic reaction to chlorhexidine in an anaesthetised patient.
Anaesth Intensive Care 1985 Nov;13(4):429-30.
7. Okano M, Nomura M, Hata S, Okada N, Sato K, Kitano Y, *et al*.
Anaphylactic symptoms due to chlorhexidine gluconate.
Arch Dermatol 1989 Jan;125(1):50-2.
8. Visser LE, Veeger JH, Roovers MH, Chan E, Stricker BH.
[Anaphylaxis caused by chlorhexidine following cystoscopy or urethral catheterization].
Ned Tijdschr Geneeskd 1994 Apr 9;138(15):778-80.
9. Knight BA, Puy R, Douglass J, O'Hehir RE, Thien F.
Chlorhexidine anaphylaxis: a case report and review of the literature.
Intern Med J 2001 Sep;31(7):436-7.
10. Stephens R, Mythen M, Kallis P, Davies DW, Egner W, Rickards A.
Two episodes of life-threatening anaphylaxis in the same patient to a chlorhexidine-sulphadiazine-coated central venous catheter.
Br J Anaesth 2001 Aug;87(2):306-8.
11. Garvey LH, Roed-Petersen J, Menne T, Husum B.
Danish Anaesthesia Allergy Centre – preliminary results.
Acta Anaesthesiol Scand 2001 Nov;45(10):1204-9.
12. Laxenaire MC.
Drugs and other agents involved in anaphylactic shock occurring during anaesthesia. A French multicenter epidemiological inquiry.
Ann Fr Anesth Reanim 1993;12(2):91-6.
13. Fisher M, Baldo BA.
Anaphylaxis during anaesthesia: current aspects of diagnosis and prevention.
Eur J Anaesthesiol 1994 Jul;11(4):263-84.
14. Garvey LH, Roed-Petersen J, Husum B.
Anaphylactic reactions in anaesthetised patients – four cases of chlorhexidine allergy.
Acta Anaesthesiol Scand 2001 Nov;45(10):1290-4.
15. Bousquet J, Flahault A, Vandenplas O, Ameille J, Duron JJ, Pecquet C, *et al*.
Natural rubber latex allergy among health care workers: a systematic review of the evidence.
J Allergy Clin Immunol 2006 Aug;118(2):447-54.
16. Barfred L, Rasmussen HH, Andersen KE.
[Incidence of hand eczema after surgical washing and use of surgical gloves].
Ugeskr Laeger 1993 Apr 26;155(17):1258-61.
17. Stingeni L, Lapomarda V, Lisi P.
Occupational hand dermatitis in hospital environments.
Contact Dermatitis 1995 Sep;33(3):172-6.
18. Rudzki E, Rebandel P, Grzywa Z.
Patch tests with occupational contactants in nurses, doctors and dentists.
Contact Dermatitis 1989 Apr;20(4):247-50.
19. Aggett PJ, Cooper LV, Ellis SH, McAinsh J.
Percutaneous absorption of chlorhexidine in neonatal cord care.
Arch Dis Child 1981 Nov;56(11):878-80.
20. Cowen J, Ellis SH, McAinsh J.
Absorption of chlorhexidine from the intact skin of newborn infants.
Arch Dis Child 1979 May;54(5):379-83.
21. Garvey LH, Roed-Petersen J, Husum B.
Is there a risk of sensitization and allergy to chlorhexidine in health care workers?
Acta Anaesthesiol Scand 2003 Jul;47(6):720-4.
22. Layton GT, Stanworth DR, Amos HE.
The incidence of IgE and IgG antibodies to chlorhexidine.
Clin Exp Allergy 1989 May;19(3):307-14.
23. Ohtoshi T, Yamauchi N, Tadokoro K, Miyachi S, Suzuki S, Miyamoto T, *et al*.
IgE antibody-mediated shock reaction caused by topical application of chlorhexidine.
Clin Allergy 1986 Mar;16(2):155-61.
24. Pham NH, Weiner JM, Reisner GS, Baldo BA.
Anaphylaxis to chlorhexidine. Case report. Implication of immunoglobulin E antibodies and identification of an allergenic determinant.
Clin Exp Allergy 2000 Jul;30(7):1001-7.
25. Heinemann C, Sinaiko R, Maibach H.
Immunological contact urticaria and anaphylaxis to chlorhexidine: overview.
exogenous dermatology 2002;1:186-94.
26. Ebo DG, Bridts CH, Stevens WJ.
IgE-mediated anaphylaxis from chlorhexidine: diagnostic possibilities.
Contact Dermatitis 2006 Nov;55(5):301-2.
27. Aalto-Korte K, Makinen-Kiljunen S.
Symptoms of immediate chlorhexidine hypersensitivity in patients with a positive prick test.
Contact Dermatitis 2006 Sep;55(3):173-7.
28. Untersmayr E, Poulsen LK, Platzer MH, Pedersen MH, Boltz-Nitulescu G, Skov PS, *et al*.
The effects of gastric digestion on codfish allergenicity.
J Allergy Clin Immunol 2005 Feb;115(2):377-82.
29. Nopp A, Johansson SGO, Ankerst J, Bylin G, Cardell LO, Gronneberg R, *et al*.
Basophil allergen threshold sensitivity: a useful approach to anti-IgE treatment efficacy evaluation.
Allergy 2006 Mar;61(3):298-302.

PhARF

Pharmacia Allergy Research Foundation
Founded in honour of the 20th anniversary of IgE 1967-1987

The objective of this Foundation is to encourage progress in allergy research through the recognition of an outstanding investigator by means of an

INTERNATIONAL AWARD of USD 50 000

This Award, characterized as a personal prize, is offered annually to a scientist, **less than 40 years of age**, who has made outstanding contributions to the field of allergy through creative and independent research efforts. The scientific achievements of the candidate should have contributed to a better understanding of allergic inflammation, as well as to improved diagnostic procedures and to improved treatment, resulting in optimal patient management.

Subject for 2007

Impact of allergy – from mechanisms to treatment

Selection of the Award recipient will be made by an International Scientific Committee, made up of internationally recognized senior scientists, today chaired by Prof Paul O´Byrne, Hamilton, ON, Canada. The judgement of the International Scientific Committee will be based on the submission of an unpublished review article, describing the research achievements and research goals of the candidate. The contribution of the recipient of the International Award and Honorable Mention will be published.

Look for advertisements in allergy and immunology journals late 2006 and beginning of 2007.

For further information and to obtain **application forms**, please, visit PhARF web site at **www.phadia.com** or contact the:

PhARF Office, attn: Marie Lantz, c/o Phadia AB, P.O. Box 6460, F35-4, SE-751 37 Uppsala, Sweden – or e-mail: marie.lantz@phadia.com

The application must be received no later than March 12, 2007

New Horizons – Allergy –

Published by Phadia AB,
P O Box 6460, SE-751 37 Uppsala,
Sweden
Editor: Maria Lundberg
Phone: +46 18 16 50 00,
Fax: +46 18 16 63 23
E-mail:
marketing.diagnostics@phadia.com