

IMMEDIATE HYPERSENSITIVITY TO CHLORHEXIDINE: LITERATURE REVIEW

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Summary

Chlorhexidine, an antiseptic belonging to family of biguanides, is used extensively in the medical and surgical environment. Late onset hypersensitivity and eczema occur regularly and are well documented events. Conversely, immediate hypersensitivity, sometimes taking the form of acute urticaria that can result in anaphylactic shock, is rarer. These manifestations can occur during contact of the skin or mucosa with chlorhexidine. Out of the fifty case reports of chlorhexidine-related anaphylaxis published worldwide over the past ten years, fifteen occurred during surgery. Signs generally appear from 15 to 45 minutes after the start of anesthesia. If there is any suspicion of immediate allergy to chlorhexidine, prick-tests or even intradermal reaction (IDR) techniques are highly recommended. In the event of confirmed allergy to chlorhexidine, strict eviction is required, bearing in mind that over a hundred medicinal products currently on the French market contain chlorhexidine.

Key-words: Chlorhexidine - Acute urticaria - Anaphylactic shock - Perioperative shock.

INTRODUCTION

Chlorhexidine is an antiseptic belonging to the family of biguanides and is used extensively in medicine and surgery: disinfection of healthy skin and mucosa, cleaning of wounds and burns, urethra lubrication before catheterization or urological investigations, vaginal lubrication, nasal spray, etc. It is added to eye drops, toothpaste and is even found in some central venous catheters. The concentration of chlorhexidine varies from 0.004% to 4% (1% corresponding to 10 mg of chlorhexidine digluconate /ml of aqueous or alcoholic solution).

Chlorhexidine may cause immuno-allergic reactions. Late onset hypersensitivity or eczema occurs in 0.1 to 0.8 % of cases (3). This clinical situation is now well known. Conversely, immediate hypersensitivity, sometimes taking the form of acute urticaria that can result in anaphylactic shock, is described more rarely. Many health care professionals know very little, of nothing, of this clinical situation.

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HISTORY AND EPIDEMIOLOGY

As early as 1972, experiments demonstrated that it was possible to induce immediate hypersensitivity to chlorhexidine in guinea pigs by administering repeated subcutaneous injections (12).

The first clinical cases of immediate reaction to chlorhexidine were reported from 1967 in Japan. Having noted fifty cases, including nine of anaphylactic shock between 1967 and 1984, the Japanese Health Ministry prohibited the use of chlorhexidine on mucosa and limited the concentration to 0.05% for skin disinfection (25).

Similarly, several state bodies recorded cases of anaphylactic shock in Denmark, the Netherlands and Great Britain: Danish Medicine Agency (5 cases reported for the period 1968-2000), Dutch Database (6 cases for the period 1983-1994), Committee on Safety of Medicine (2 cases for the period 1965-1996) (8).

The first case of perioperative anaphylactic shock was reported in 1984 by Nishioka (23). Out of the fifty cases of anaphylactic shock related to chlorhexidine published worldwide over the past ten years, about fifteen occurred during surgery (5, 8, 17, 27, 29, 31, 35,

36, 41). In France, for the period 1985-2000, the GERAP (Groupe d'Etude et de Recherche en Anesthésie Per opératoire) reported only two cases of chlorhexidine-induced anaphylactic shock out of the 4,919 cases of peroperative anaphylactic shock, i.e. 0.05% (19).

CLINICAL PICTURES AND CIRCUMSTANCES OF ONSET

CLINICAL PICTURES

Within minutes of contact with skin or mucosa, a sensitized subject presents a clinical picture associating contact urticaria which may become generalized, angioedema, bronchospasm or even anaphylactic shock of varied intensity.

CIRCUMSTANCES OF ONSET

The exact circumstances of chlorhexidine use must be identified: contact may be with healthy skin (aseptic procedures), or a lesion (dressing a burn or a wound) (2, 4, 6, 7, 24, 25, 27, 34, 37) containing chlorhexidine was reported and two publications report anaphylactic shock after vaginal instillation of chlorhexidine whilst placing an intrauterine device or during conization of the cervix (26, 30, 42). Thune described the case of an anaphylactic reaction in a man using an antiseptic dental gel (39).

However, the most frequently reported cases document anaphylaxis after lubrication of the urethra with a chlorhexidine gel associated with an anesthetic (Instillagel®) during urinary catheterization or urological examinations (8, 13, 14, 17, 20, 31, 32, 40, 41, 43), and also after placing central venous catheters that are coated with chlorhexidine (not marketed in France) (11, 22, 28, 35, 36, 38).

PEROPERATIVE ANAPHYLACTIC SHOCK

Peroperative anaphylactic shock can sometimes be very serious (5, 8, 17, 27, 29, 32, 35, 36, 41).

Chlorhexidine is used extensively during surgery: disinfection of the surgical field, skin disinfection before placing a venous or arterial catheter or before an epidural, lubrication of the urethra before catheterization or any invasive urological procedure, etc.

Signs generally appear after the start of anesthesia, i.e. from 15 to 45 minutes and include hypotension, skin rash or generalized urticaria, tachycardia, bronchospasm, sometimes severe anaphylactic shock resulting in cardiovascular collapse or cardiac arrest. In

some cases, plasma tryptase is increased during shock indicating mastocyte degranulation (8, 41).

In some patients, it is not rare to find history of reactions to chlorhexidine which should have suggested hypersensitivity to the compound: urticaria or rash (4, 14, 41), malaise classed as vaso-vagal (8) or even recurrent anaphylactic shocks (8, 17, 29, 32, 37). Sometimes eczema precedes immediate hypersensitivity (5, 39).

ALLERGY TESTING

Allergy testing starts by analysing clinical signs, studying the chronology of events in the context of the allergic incident, collecting information on the different medications administered before anaphylaxis as well as those prescribed during anaphylaxis, and finally, noting the results of any laboratory tests carried out in the emergency (plasma tryptase and histamine) (16, 33).

In the event of peroperative shock, ideally one should have access to a copy of the hospital file and the anesthesia report sheet.

Within six weeks of the allergic reaction, allergy testing is carried out against the suspected medications (33). If any hypersensitivity to chlorhexidine is found, skin tests (skin-prick tests and intradermal reaction tests) and laboratory tests are performed. However, certain publications do not specify the test techniques used, and some use scratch-tests (25).

PRICK-TESTS

Allergy testing always starts with prick-tests with a solution of chlorhexidine gluconate. The reaction threshold varies but can appear at very low concentrations of chlorhexidine: 1% (14), 0.5% (8, 39), 0.05% (39), 0.005% (37), 0.002% (2), 0.0005% (43). Autengarten and Torricelli performed control tests on three and ten patients respectively (2, 37); prick-tests remain negative at the 0.05% or even 0.002% concentration. Very recently, Garvey did an epidemiological survey on the risk of sensitization to chlorhexidine in the medical environment and found no positive prick-test with the 0.5% concentration in 104 subjects tested (9).

Thus, in the event of severe anaphylactic reaction, testing should be started with a low concentration of chlorhexidine (0.005 or even 0.0005%).

INTRADERMAL REACTION (IDR) TESTS

If prick-tests are negative, some authors recommend IDR tests (8, 42). Garvey reports reactivity at the concentration of 0.0002% and Yong at 0.0005% (8,

42). A recent study carried out by Garvey and quoted above, detects no positive IDR out of the 104 tested subjects at the concentration of 0.0002% (9). Okano even reports negative IDR in ten controls at the 0.005% concentration (25).

LABORATORY TESTS

Specific IgEs can be identified using a RAST type radio-immunological technique by fixing a chlorhexidine-HSA (human serum albumin) complex on cellulose (15, 24), or other techniques using different supports to fix chlorhexidine (sepharose). These techniques are still in the clinical research phase and are not used routinely even if some publications refer to specific IgE detection without specifying the technique used (41).

The antigenic determinant of chlorhexidine remains unknown. Pham suggests the hypothesis that the entire molecule may be involved (29). It can be noted that an antimalarial drug, proguanil (Paludrine®), is the monovalent compound of chlorhexidine: the association of the two molecules of proguanil corresponds to one molecule of chlorhexidine.

WHAT TO DO IN THE EVENT OF ALLERGY TO CHLORHEXIDINE?

In the event of confirmed allergy to chlorhexidine, strict eviction is required, bearing in mind that over a hundred medicinal products currently on the French market contain chlorhexidine. Other antiseptics can be used but contact eczema is always possible. Exceptionally, povidone iodine (Betadine®), like chlorhexidine, can also cause anaphylaxis (1, 10, 18, 21).

CONCLUSION

Immediate allergy to chlorhexidine is a rare clinical situation but must be borne in mind. Indeed, anaphylactic shock is often preceded by signs suggesting immediate hypersensitivity to chlorhexidine that should be identified. In the event of late-onset peroperative anaphylactic shock in relation to start of anesthesia, the role of antiseptics must be borne in mind even if initial allergy test results were negative. If there is any suspicion of immediate allergy to chlorhexidine, prick-tests or IDR tests are highly recommended.

BIBLIOGRAPHY

1. Adachi A., Fukunaga A., Hayashi K., Kunisada M., Horikawa T. - Anaphylaxis to polyvinylpyrrolidone after vaginal application of povidone-iodine. *Contact Dermatitis* 2003;48:133-6.

2. Autegarten J.-E., Pecquet C., Huet S., Bayrou O., Leynadier F. - Anaphylactic shock after application of chlorhexidine to unbroken skin. *Contact Dermatitis* 1999;40:215.
3. Barbaud A. - Dermites de contact aux antiseptiques. *Progrès en Dermato-allergologie. GERDA Dijon 2002*, John Libbey Eurotext Editeur, Paris, 73-84.
4. Cheung J., O'Leary J.-J. - Allergic reaction to chlorhexidine in an anaesthetised patient. *Anaesth Intensive Care* 1985;13:429-30.
5. Ebo D.-G., Stevens W.-J., Bridts C.-H., Matthieu L. - Contact allergic dermatitis and life-threatening anaphylaxis to chlorhexidine. *J Allergy Clin Immunol* 1998;101:128-9.
6. Evans R.-J. - Acute anaphylaxis due to topical chlorhexidine acetate. *BMJ* 1992;304:686.
7. Fujita S., Sumita S., Kawana S., Iwasaki H., Namiki A. - Two cases of anaphylactic shock induced by chlorhexidine. *Masui* 1997;46:1118-21.
8. Garvey L.-H., Roed-Petersen J., Husum B. - Anaphylactic reactions in anaesthetised patients - Four cases of chlorhexidine allergy. *Acta Anaesthesiol Scand* 2001;45:1290-4.
9. Garvey L.-H., Roed-Petersen J., Husum B. - Is there a risk of sensitization and allergy to chlorhexidine in health care workers? *Acta Anaesthesia Scand* 2003;47:720-4.
10. Gonzalo Garijo M.-A., Duran Quintana J.-A., Bobadilla Gonzalez P., Maiquez Asuero P. - Anaphylactic shock following povidone. *Ann Pharmacother* 1996;30:37-40.
11. Harukuni I., Ishizawa Y., Nishikawa T., Takeshima R., Dohi S., Naito H. - Anaphylactic shock with ventricular fibrillation induced by chlorhexidine. *Masui* 1992;41:455-9.
12. Haugen E., Johansen J.-R. - Sensitization of guinea pigs with chlorhexidine. *Acta Odont Scand* 1974;32:173-5.
13. Jayathillake A., Mason D.-F., Broome K. - Allergy to chlorhexidine gluconate in urethral gel : report of four cases and review of literature. *Urology* 2003;61:836-7.
14. Knight B.-A., Puy R., Douglass J., O'Hehir R.-E., Thien F. - Chlorhexidine anaphylaxis : a case report and review of literature. *Intern Med J* 2001;31:436-7.
15. Layton G.-T., Stanworth D.-R., Amos H.-E. - The incidence of IgE and IgG antibodies to chlorhexidine. *Clin Exp Allergy* 1989;19:307-14.
16. Larache D., Guilloux L., Gueant J.-L. - Diagnostic of anaphylactoid reactions : *in vitro* tests. *Ann Fr Anesth Reanim* 2002; 21 (suppl 1):73-96.
17. Lockhart A.-S., Harle C.-C. - Anaphylactic reactions due to chlorhexidine allergy. *Br J Anaesth* 2001;87:940-1.
18. Lopez Saez M.-P., De Barrio M., Zubeldia J.-M., Prieto A., Olalde S., Baeza M.-L. - Acute IgE-mediated generalized urticaria-angioedema after topical application of povidone-iodine. *Allergol Immunopath* 1998;26:23-6.
19. Mertes P.-M., Laxenaire M.-C., Alla F. - Anaphylactic and anaphylactoid reactions during occurring anesthesia in France in 1999-2000. *Anesthesiology* 2003;99:536-45.
20. Mitchell D.-J., Parker F.-C. - Anaphylaxis following urethral catheterisation. *Br J Urol* 1993;71:613.
21. Nakao M., Nakatani K., Suyama H., Maekawa T., Nakagawa M., Hanaki C., Kawaguchi R. - A case of life threatening anaphylactoid reaction caused by povidone-iodine. *Masui* 1997;46:105-9.
22. Nikaido S., Tanaka M., Yamoto M., Minami T., Akatsuka M., Mori H. - Anaphylactoid shock caused by chlorhexidine gluconate. *Masui* 1998;47:330-4.
23. Nishioka K., Doi T., Katayama I. - Histamine release in contact urticaria. *Contact Dermatitis* 1984;11:191.
24. Ohtoshi T., Yamauchi N., Tadokoro K., Miyachi S., Suzuki S., Miyamoto T., Muranaka M. - IgE antibody-mediated shock reaction caused by topical application of chlorhexidine. *Clin Allergy* 1986;16:155-6.
25. Okano M., Nomura M., Hata S., Okada N., Sato K., Kitano Y., Tashiro M., Yoshimoto Y., Hama R., Aoki T. - Anaphylactic symptoms due to chlorhexidine gluconate. *Arch Dermatol* 1989;125:50-2.
26. Okuda T., Funasaka M., Arimitsu M., Umeda T., Wakita K., Koga Y. - Anaphylactic shock by ophthalmic wash solution containing chlorhexidine. *Masui* 1994;43:1352-5.
27. Peutrell J.-M. - Anaphylactoid reaction to topical chlorhexidine during anaesthesia. *Anaesthesia* 1992;47:1013.

28. Pittaway A., Ford S. - Allergy to chlorhexidine-coated central venous catheters revisited. *BJA* 2002;88:304-5.
29. Pham N.-H., Weiner J.-M., Reisner S., Baldo B.-A. - Anaphylaxis to chlorhexidine. Case report. Implication of immunoglobulin E antibodies and identification of an allergenic determinant. *Clin Exp Allergy* 2000;30:1001-7.
30. Porter B.-J., Acharya U., Ormerod A.-D., Herriot R. - Latex/chlorhexidine-induced anaphylaxis in pregnancy. *Allergy* 1998;53:455-7.
31. Ramselaar C.-G., Craenen A., Bijleveld R.-T. - Severe allergic reaction to an intra-urethral preparation containing chlorhexidine. *Br J Urol* 1992;70:451-2.
32. Russ B.-R., Maddern P.-J. - Anaphylactic reaction to chlorhexidine in urinary catheter lubricant. *Anaesth Intensive Care* 1994;22:611-2.
33. Société Française d'Anesthésie et de Réanimation (French Society for Anaesthesia and Intensive Care) - Reducing the risk of anaphylaxis during anaesthesia. Abbreviated text. *Ann Fr Anesth Reanim* 2002;21 (suppl. 1):7-23.
34. Snellman E., Rantanen T. - Severe anaphylaxis after a chlorhexidine bath. *J Am Acad Dermatol* 1999;40:771-2.
35. Stephens R., Mythen M., Kallis P., Davies D.-W., 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;87:306-8.
36. Terazawa E., Shimonaka H., Nagase K., Masue T., Dohi S. - Severe anaphylactic reaction due to chlorhexidine-impregnated central venous catheter. *Anesthesiology* 1998;89:1296-8.
37. Torricelli R., Wüthrich B. - Life-threatening anaphylactic shock due to skin application of chlorhexidine. *Clin Exp Allergy* 1996;26:112.
38. Toshiyuki O., Junichiro H., Kanda N., Mikami K. - Anaphylactic shock induced by an antiseptic-coated central nervous catheter. *Anesthesiology* 1997;87:1242-4.
39. Thune P. - Two patients with chlorhexidine allergy-anaphylactic reaction and eczema. *Tidsskr Nor Lægeforen* 1998;118:3295-6.
40. Visser L.-E., Veeger J.-H., Roovers M.-H., Chan E., Stricker B.-H. - Anaphylaxis caused by chlorhexidine following cystoscopy or urethral catheterisation. *Ned Tijdschr Geneesk* 1994;138:778-80.
41. Wicki J., Deluze C., Cirafici L., Desmeules J. - Anaphylactic shock induced by intraurethral use of chlorhexidine. *Allergy* 1999;54:768-9.
42. Wong W.-K., Goh C.-L., Chan K.-W. - Contact urticaria from chlorhexidine. *Contact Dermatitis* 1990;22:52.
43. Young D., Parker F.-C., Foran S.-M. - Severe allergic reactions and intra-urethral chlorhexidine gluconate. *Med J Australia* 1995;162:257-8.

