Allergy to chlorhexidine: beware of the central venous catheter

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Abstract: The example reported here illustrates the frequent belief that "innocent" products such as central venous catheters do not produce allergic reactions. However, they might be impregnated with chlorhexidine and elicit serious life-threatening anaphylaxis in patients with allergy to this antiseptic agent.

Key words: Allergy; chlorhexidine; central venous catheter.

Case report

A 53-year-old man was referred to our outpatient clinic of immunology and allergology because of an anesthesia related anaphylaxis. The episode was characterized by a severe bronchospasm, severe hypotension and transient ST-segment elevations in all precordial leads of the electrocardiogram. Onset-of reaction was early, in so far as it occurred within 5 minutes after induction with propofol, sufentanyl and cisatracurium. The surgical procedure, namely a nephrectomy, was aborted and the patient was successfully treated using epinephrine, antihistaminic agents, glucocorticosteroids, and colloid fluid loading. The early measured serum tryptase level revealed to be 31.5 µg/L (normal <11.5, ImmunoCAP, Thermo-Fisher Scientific, Uppsala, Sweden).

The medical past history of the patient was unremarkable. Six weeks after the acute episode, blood analysis showed a normal blood cell count, a normal complement profile, and normalized serum tryptase levels at 3.6 µg/L. At that time, the total immunoglobulin E (IgE) concentration was 66.5 kU/L (ImmunoCAP). The concentration of specific IgE's for chlorhexidine was 0.72 kUA/L (normal <0.1 kUA/L), while Specific IgE's for latex, atracurium, rocuronium, morphine, atracurium, ethylene oxide and poppy seed (Papaver somniferum) were negative. Skin tests were also performed and sought at reactions against latex (Stallergenes, Fresnes, France), 2% chlorhexidine digluconate in 70% alcohol (start dilution 10^-2 up to commercial stock solution), serial dilutions of the 5 afore-mentioned neuromuscular blocking agents (rocuronium, vecuronium, atracurium, cisatracurium, and suxamethonium), and 2% chlorhexidine digluconate (Hibidil, 50 µg/mL in 0.5% alcohol) in activating dilutions of 0.5 to 5 µg/mL were tested in the basophil activation buffer (1, 3). Except for chlorhexidine, which provoked a wheal and flare reaction of respectively 5 and 10 mm on the skin, all skin tests were negative.

Analysis of in vitro basophil activation was also performed as described earlier (1, 3). In this technique, the identification and activation of basophils relies upon the recognition of specific surface markers by fluorochrome-conjugated monoclonal antibodies, and results are expressed as the percentage of CD63 positive basophils. Anti-IgE (Pharmingen, BD Bioscience, Erembodegem, Belgium) as a positive control, stimulation buffer as a negative control, serial dilutions of the 5 afore-mentioned neuromuscular blocking agents (rocuronium, vecuronium, atracurium, cisatracurium, and suxamethonium), and 2% chlorhexidine digluconate (Hibidil, 50 µg/mL in 0.5% alcohol) in activating dilutions of 0.5 to 5 µg/mL were tested in the basophil activation buffer (1, 3). Figure 1 shows the results obtained in our patient. We observed an up-regulation of CD63 expression from 1% (spontaneous) up to 58% with 0.5 µg/mL chlorhexidine.

According to these findings, a diagnosis of an IgE-mediated allergy to chlorhexidine was made. Revision of the anesthetic procedure record revealed...
that the exposure to this antiseptic agent occurred during disinfection of the insertion site of the central venous catheter using Hibitane®, as well as during the insertion of the urine catheter and the application of a chlorhexidine-containing urethral lubricant. One week later, the nephrectomy was scheduled again. In light of the evidenced chlorhexidine allergy, all antiseptics and lubricants containing chlorhexidine were carefully removed from the theater. Despite those precautions, the patient presented a second anaphylactic reaction with severe hypotension and transient ST-segment elevations in all precordial leads, almost immediately after the insertion of the central venous catheter (ARROW g'ard Blue REF CV-27702-E, International Teleflex Medical). The antiseptic agent used for that insertion was povidone-iodine (Iso-betadine®), and anesthesia of the skin was performed using lidocain (Xylocaine®). The anesthetic and surgical procedures were postponed again. Close inspection of the packaging disclosed that the central venous catheter had been extra-luminary coated with chlorhexidine. No further confirmatory testing was undertaken.

**DISCUSSION**

Chlorhexidine, a cationic bisguanide antiseptic agent, is used as a (di)acetate or (di)gluconate salt. Chlorhexidine salts can trigger irritant dermatitis, allergic contact dermatitis (4-6) and immediate IgE-mediated allergic reactions (1, 4, 5, 7-9). Those allergic reactions were first described in 1984 (10). The exact prevalence of chlorhexidine-associated anaphylactic reactions occurring in the course of anesthetic procedures remains unknown, but is likely to be underestimated. During a 10-year period, only 50 cases of chlorhexidine anaphylactic reactions were reported worldwide (8). Noteworthy, no single case was reported in the 9 French surveys on anesthesia-related anaphylaxis, which currently include data of more than 3500 patients that were collected between 1997 and 2007 (11, 12). In contrast, an IgE-mediated chlorhexidine allergy has been documented in 12 out of 174 (7%) Danish patients (9), and in 22 out of 344 (6.4%) patients from the Flemish part of Belgium (own unpublished data). All had been referred because of suspected allergic reactions in connection with anesthesia or surgery. Of note, iodinated povidone is by far less incriminated in immediate allergic reactions than chlorhexidine (e.g. no cases in our series).

To our knowledge, the first case of anaphylactic reaction related to a chlorhexidine-coated central venous catheter has been reported in 1997 by Oda et al. (13) in Japan. Four years later, the first European case has been reported by Stephens et al. (14). Since then, approximately 10 cases have been documented and published (15-19). In 1998, the Food and Drug Administration issued an alert to the medical community about the potential of severe allergic reactions to chlorhexidine-impregnated medical devices (20) (http://www.fda.gov/medicaldevices/safety/alertsandnotices/publichealthnotifications/ucm062306.htm). Examples of such medical devices are numerous (Table 1).

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Fig. 1. — Representative plots of the basophil activation test with chlorhexidine. Basophils are identified as HLA-DR negative and CD123 positive cells. 58% of the basophils are CD63 positive after activation with chlorhexidine 0.5 µg/mL.
These reactions generally occur soon after the insertion of the catheter, and are generally severe with profound hypotension and cardiovascular collapse requiring advanced life support. Despite the close relationship between the two events, namely the catheter insertion and the occurrence of the allergic reaction, the fact that central venous catheters might be impregnated with allergens such as latex, antibiotics and chlorhexidine (21-25) does not spontaneously come to the mind of anesthesia practitioners. As illustrated here, such anaphylactic reactions secondary to a central venous catheter insertion may still occur (15, 18), despite the previous identification of a chlorhexidine allergy (14, 17, 19). Therefore, in the context of anesthesia-related anaphylaxis, we recommend that attending anesthesiologists closely inspect the package labels and inserts for potential warnings of all applied medical devices in order to be aware of the presence of potential allergens such as latex, antiseptic agents and antibiotic agents. Those verifications should particularly be performed when a patient exhibits an unexplained allergic reaction. Finally, our case further emphasizes the importance of an increased tryptase level at the time of the reaction at prompting a meticulous search for hidden allergens in patients with a negative diagnostic investigation. Actually, allergologists will orient their diagnostic tests according from clinical suspicion to correct diagnosis, Allergy, 66 (8), 1014-9, 2011.

References