

Anaphylaxis to Chlorhexidine-Coated Central Venous Catheters: A Case Series and Review of the Literature

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Abstract

Background: Anaphylactic reactions to chlorhexidine are rare but are being reported increasingly in association with a variety of products.

Methods: We report three cases of anaphylaxis to chlorhexidine in patients presenting for cardiac surgery.

Results: In each case, anaphylaxis was precipitated by the insertion of a central venous catheter impregnated with chlorhexidine acetate. Subsequent investigations confirmed chlorhexidine as the causal agent.

Conclusion: Extensive use of chlorhexidine to reduce hospital-acquired infections has the potential to sensitize a small proportion of patients, leading to life-threatening anaphylaxis on subsequent exposure.

CHLORHEXIDINE is used widely in healthcare settings for skin antisepsis prior to venipuncture and insertion of vascular catheters, as a shampoo/body wash to reduce the microbial bio-burden prior to surgery, and as a coating on central venous catheters (CVCs) to reduce rates of infection. Chlorhexidine products are recommended increasingly to reduce infection risks for patients. American guidelines for the prevention of central line-associated blood stream infection (CLABSI) recommend 2% chlorhexidine for skin antisepsis prior to catheter insertion [1], and Darouiche et al. [2] demonstrated recently the superior efficacy of chlorhexidine skin antisepsis compared with povidone-iodine for reducing surgical site infections. As chlorhexidine gains broader use, surgical patients are being exposed repeatedly to the chemical during preoperative procedures, but minor hypersensitivity reactions often go unnoticed or are not attributed to chlorhexidine. Subsequent exposure may then lead to life-threatening anaphylaxis. We report three such cases seen within a 12-month period at a cardiac center in a large acute-care hospital.

Case Reports

Case 1

A 71-year-old man who presented with chest pain was found to have severe left mainstem and three-vessel coronary artery disease by coronary angiography. On the day of

scheduled coronary artery bypass grafting (CABG), the patient had a preparatory cleansing shower with a 4% chlorhexidine soap solution, during which he developed a generalized pruritic maculopapular rash. This rash subsided after administration of intravenous chlorpheniramine and hydrocortisone. Six hours later, he underwent induction of anesthesia followed by multi-lumen CVC placement under full aseptic conditions. The drugs given at induction were etomidate, pancuronium, fentanyl, cefuroxime, and hydrocortisone. Immediately after CVC placement, the patient became profoundly hypotensive and required aggressive resuscitation with epinephrine and fluids. Surgery was abandoned. Over the succeeding 24 h, serial serum tryptase concentrations peaked at 131 mcg/mL (normal range 2–14 mcg/mL), confirming substantial mast cell degranulation. A plasma immunoglobulin E (IgE) test for latex hypersensitivity was negative. Intradermal testing for pancuronium hypersensitivity was positive, and this drug therefore was considered the most likely antigenic trigger. Concurrent intradermal testing with chlorhexidine at a 1:100 dilution (0.005%) generated an 8-mm wheal; at that time, the irritant-inducing concentration of chlorhexidine had not been established. It is now known that a positive intradermal test at 0.005% is indicative of hypersensitivity.

The patient was readmitted for CABG one month later. The preoperative shower with chlorhexidine was omitted, and

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povidone-iodine (10% povidone-iodine plus 95% methylated spirit; Videne®, Ecolab®, Swindon, Wiltshire, UK) was used for skin preparation prior to peripheral venous and arterial cannulation. After CVC insertion under local anesthesia and before administration of any other intravenous agent, severe, life-threatening hypotension developed again, and the patient had to be resuscitated aggressively. Serial tryptase concentrations over the next 24 h peaked at > 200 mcg/mL. On further review of all potential triggers, it was determined that the skin preparation used pre-cannulation at the time of the patient's first allergic collapse contained chlorhexidine. It also was confirmed that the multi-lumen CVC inserted on each occasion was coated with chlorhexidine and silver sulfadiazine (ARROWgard® Blue Catheter, Arrow® International [Teleflex® Medical], Research Triangle Park, NC). This information was not readily apparent from the combined catheter insertion package. The patient's serum was tested for specific IgE to chlorhexidine and found to be positive at 7.4 kU/L (normal reference value < 0.35 kU/L). After joint review by the cardiologists and cardiac surgeons, the decision was made to postpone the patient's surgery indefinitely. He subsequently underwent successful and uneventful staged multi-vessel percutaneous coronary artery stenting, initially of the right coronary artery and subsequently of the left main coronary artery. This was performed under local anesthesia, using alcohol for skin preparation and non-antiseptic-impregnated sheaths for vascular access.

Case 2

A 26-year old patient presented for investigation of absent lower limb pulses and was found to have a bicuspid aortic valve, an aortic root aneurysm, and aortic coarctation. He underwent successful surgery to bypass the aortic coarctation and five weeks later was readmitted for aortic valve and root replacement. After a pre-operative shower with 4% chlorhexidine shower gel, he developed a purpuric rash that resolved spontaneously without treatment. Prior to induction of general anesthesia, a peripheral venous catheter and a radial artery catheter were inserted via the left hand after skin preparation using 2% chlorhexidine. The patient complained of itching of his left hand. General anesthesia was induced with midazolam, fentanyl, propofol, and rocuronium. Following this, a chlorhexidine-coated CVC was inserted, which precipitated anaphylactic shock. The patient was resuscitated with inotropes and fluids, and the surgery was postponed. Serial mast cell tryptase concentrations over a period of 24 h peaked at 35.2 mcg/mL, confirming anaphylaxis. Further investigations revealed positive skin prick and intradermal testing to chlorhexidine and a chlorhexidine-specific IgE concentration of 0.40 kU/L. The patient underwent uneventful surgery two weeks later using an iodine-based skin preparation and a non-antimicrobial catheter.

Case 3

A 73-year-old patient who presented with a history of angina and a positive exercise stress test was found to have complex trifurcational left anterior descending coronary artery disease. After a coronary angiogram, a minor cutaneous allergic reaction was noted at the site of the femoral sheath, which had been inserted after cleansing with 2% chlorhexidine. The allergic reaction resolved after administration of

intravenous chlorpheniramine and hydrocortisone. On the day of scheduled CABG, the patient had a pre-operative shower with a chlorhexidine soap solution with no signs or symptoms of an allergic reaction. After the induction of general anesthesia using fentanyl, propofol, pancuronium, and cefuroxime and the insertion of a chlorhexidine-coated CVC, he developed anaphylactic shock. Initial resuscitation with inotropes and fluids failed. The patient was placed on emergency cardiopulmonary bypass, and the planned coronary artery surgery was performed. The CVC was changed to a chlorhexidine-free catheter. His serial mast cell tryptase concentration peaked at 114 mcg/L, and the chlorhexidine-specific IgE concentration was 4.62 kU/L. The patient ultimately made a good recovery after a long stay in the intensive care unit.

Discussion

The precise incidence of anaphylactic reactions to chlorhexidine is unknown, but the Danish Anesthesia Allergy Center reports that chlorhexidine was the causative agent in 10% to 15% of positive reactions in patients investigated after suspected anaphylactic reactions during anesthesia [5]. Because of the rarity of anaphylactic reactions associated with chlorhexidine, information in the medical literature is confined to case studies of individuals or small groups of patients, such as the cases presented here. The case study format is a less formal way of reporting events than descriptions of adverse events in large clinical trials. As such, the amount and specificity of information available about individual cases varies substantially.

Acute anaphylactic shock during anesthesia has been reported in Japanese and European patients following insertion of chlorhexidine-impregnated CVCs [6–11]. In one case, chlorhexidine was not identified as the causative agent until two months after surgery, the discovery being made as the result of a positive intradermal test [11]. Severe allergic hypersensitivity has been reported at induction of anesthesia for CABG on only one previous occasion [9]. In this case, the patient had prior exposure to chlorhexidine gluconate (CHG) solution (Savlon®, Novartis Consumer Health, Horsham, United Kingdom) for skin antisepsis in preparation for an angiogram. In patients undergoing cardiac surgery, the implications of hemodynamic collapse secondary to allergic hypersensitivity clearly are grave. According to the medical literature, anaphylaxis associated with chlorhexidine used for topical skin antisepsis prior to surgery or for wound disinfection is more common than that associated with CHG-impregnated CVCs, although still relatively rare. In a publication by Okano et al., six patients developed urticaria, dyspnea, and anaphylactic shock secondary to topical application of CHG solution in concentrations ranging from 0.05% to 1% [12]. Chlorhexidine gluconate was confirmed as the causative agent of type I hypersensitivity by intradermal, scratch, and epicutaneous tests. Two of the six patients had prior exposure to CHG before manifestation of anaphylaxis. Symptoms occurred during or immediately after surgery in which CHG had been applied to the skin or mucous membranes. Garvey et al. reported that four patients who had serious allergic reactions related to surgery and general anesthesia tested positive for CHG via skin prick and intradermal tests [8]. Symptoms appeared 20 to 40 min into the

operation, and all four patients required treatment with epinephrine. The concentration of CHG was not specified in these cases. Thong et al. described an acute hypersensitivity reaction occurring in a patient in the post-anesthesia care unit [13]. Skin testing suggested sensitivity to chlorhexidine, which had been applied over the vaginal mucosa at the end of surgery. The concentration of chlorhexidine was not specified. Other reported episodes of chlorhexidine-associated anaphylaxis have been associated with 0.05% CHG used for disinfection of foot wounds [14] and local disinfection prior to digital rectal examination [15]. Anaphylactic reactions reported in these cases included generalized urticaria, angioedema, wheezing, dizziness, vomiting, diarrhea, faintness, chest tightness, facial and lip swelling, and hypotension. Five additional cases have been related to CHG lubricant gels and creams and 0.05% chlorhexidine bath solution [11,16–18]. In each case, chlorhexidine was not identified initially as the causative allergen but was confirmed later to be responsible through skin testing in three of the five cases.

In the cases reported here associated with the use of chlorhexidine-coated CVCs, a detailed review of the case notes revealed that each patient had been exposed to topical chlorhexidine at an earlier stage of the pre-surgical investigative pathway and had evidence of minor cutaneous reactions that were not ascribed to chlorhexidine at the time. Hypersensitivities are recorded pre-operatively and before interventions as a standard of care. In this cardiac center, all care bundle interventions include chlorhexidine-coated CVCs; however, these products were introduced independent of a specific need, such as a high CRBSI rate. The chlorhexidine-coated CVCs were removed from use in the cardiac center after the third anaphylactic incident.

Chlorhexidine is used extensively in healthcare products, including pre-operative shower solutions and antiseptic skin preparations, and also is bonded to devices such as surgical mesh, dressings, and the outer surfaces of urinary and intravenous catheters. Chlorhexidine also is a component of several commercial products such as mouthwashes, dental gels, contact lens solutions, toothpastes, moisturizers, and lubricants. Given the extensive use of products containing chlorhexidine in the community and in the healthcare setting, there is potential for allergic sensitization of a proportion of patients. As noted in the review of case studies, chlorhexidine can cause the full spectrum of allergic reactions, ranging from contact dermatitis [9,15,19] to generalized urticaria [12,14,15,20] and life-threatening allergic hypersensitivity [12,18,21]. However, minor allergic reactions may be overlooked or not ascribed to chlorhexidine, resulting in potentially severe hypersensitivity reactions in patients with prior exposure [14,19,22]. Practice guidelines published by the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) suggest taking a careful medical history focusing on prior adverse reactions [23]. Any prior medication reactions increase the likelihood of adverse reactions, and multiple previous medication reactions are a greater risk. Atopic patients might be at heightened risk because of either more reactions or, more often, increased severity of reactions. According to the AAAAI/ACAAI guidelines, anaphylaxis often produces signs and symptoms within minutes of exposure to a stimulus, but some reactions develop later (e.g., > 30 min after exposure). Late-phase or

biphasic reactions can occur 8 to 12 h after the initial attack. When no prior sensitivity reaction has occurred or no information is available for a patient, it is necessary to be prepared, as hemodynamic collapse can occur rapidly with little or no cutaneous or respiratory manifestations [23]. Therefore, it is particularly important for healthcare professionals to recognize the possibility of multiple exposures to chlorhexidine within a single patient because of its greater use in medical products.

Conclusion

Patients booked for cardiac surgery receive multiple exposures to chlorhexidine during their pre-operative investigations and preparation. The use of chlorhexidine in healthcare settings has increased substantially following the universal drive to reduce the incidence of hospital-acquired infections. The root-cause analysis of these cases indicates that repeated exposure to chlorhexidine sensitized these patients, and delayed minor cutaneous reactions were not ascribed to chlorhexidine hypersensitivity. Subsequent exposure caused by chlorhexidine-coated CVCs precipitated anaphylaxis.

Greater awareness of this rare but potentially fatal outcome of chlorhexidine hypersensitivity is needed. Chlorhexidine should be considered a potential trigger for hypersensitivity reactions of various severities encountered in any healthcare setting. Vascular access catheters coated with chlorhexidine should be clearly identifiable from their packaging and avoided in all patients with a suspicion of chlorhexidine hypersensitivity. Allergic reaction to chlorhexidine must be documented clearly in patients' case notes and recorded on their wristbands prior to surgery or other invasive procedures where antiseptic skin preparations may be employed or chlorhexidine-coated catheters inserted. Identified chlorhexidine-hypersensitive patients must be cautioned regarding chlorhexidine-containing commercial products such as soaps, creams, oral rinses, or jellies, as well as lubricants used by dentists or in general practice. Any of these products may act as sensitizers and triggers of full-blown allergic hypersensitivity. Patients with proven immunologic hypersensitivity should be encouraged to wear a warning talisman conveying the message "allergic to chlorhexidine." The policy of using chlorhexidine-coated CVCs should be reviewed, as their benefits are questionable [24].

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