

Severe Anaphylaxis: The Secret Ingredient

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In this case report, we describe a healthy urological patient who suffered severe intraoperative anaphylaxis to chlorhexidine, an ingredient contained in frequently used lubricants (Instillagel®, Endosgel®). Chlorhexidine is a well-known skin disinfectant and antiseptic component in mouth-wash or other over the counter antiseptic pharmaceuticals. There is little awareness that commonly used lubricants may contain hidden chlorhexidine. After severe intraoperative anaphylaxis, it is important to investigate all potential (including hidden) agents that might have caused this life-threatening reaction. (A&A Case Reports. 2014;2:34–6.)

An anaphylactic reaction is defined as a severe, life-threatening, systemic, hypersensitivity reaction that is mediated by an immunological mechanism triggered by antigen–antibody (immunoglobulin [Ig]E, IgG) interaction or immune complexes.¹ The incidence of anaphylaxis during anesthesia is 1:5000 to 1:20,000, depending on the definition and degree of underreporting.^{1–3} In anesthesia, 60% of all severe allergic reactions are triggered by neuromuscular blocking drugs. Other frequent causes are latex (20%), antibiotics (15%), and colloids (5%).¹ Among disinfectants, chlorhexidine and povidone-iodine are the most prominent.^{1,4}

Here, we report the occurrence of a severe intraoperative anaphylaxis to an ingredient in widely used lubricants (Instillagel®, Melisana AG, Switzerland; Endosgel®, Farco-Pharma, Germany), that is, chlorhexidine.

The patient reviewed this report and gave written permission for publication.

CASE DESCRIPTION

A 45-year-old ASA physical status I man with a large kidney stone was scheduled for percutaneous nephrolitholapaxy under general anesthesia (first procedure). Apart from an uncomplicated tonsillectomy as a child, he had no significant medical history and had no known allergies. General anesthesia was induced and maintained using thiopental, fentanyl, rocuronium, and sevoflurane. Routine antibiotic prophylaxis, amoxicillin/clavulanic acid 1.2 g IV was given, and the patient's condition was stable until surgery started 30 minutes later.

After disinfecting the surgical field with povidone-iodine (Betadine®; Mundipharma Medical Company, Switzerland), his bladder was inspected with a cystoscope and a urinary catheter inserted. The renal pelvis was percutaneously punctured, and iodine-containing contrast media (Hexabrix®, Guerbet AG, Switzerland) was injected. At this time, his arterial blood pressure decreased to a minimum

of 75/40 mm Hg but returned toward normal at the next measurement. Three minutes later, his airway pressure suddenly increased, and the capnogram changed notably, suggesting bronchoconstriction. His SpO₂ decreased to 88%, and the patient became severely hypotensive (50/30 mm Hg). In addition, a progressive swelling of his tongue was noted. The operation was stopped, and a generalized erythema was visible after the drapes were removed. Treatment was initiated with epinephrine (50 mcg bolus IV, followed by an epinephrine infusion), an antihistamine (clemastine 2 mg IV), and hydrocortisone (200 mg IV). Ten minutes later, his respiratory symptoms and hemodynamics improved, and the epinephrine infusion was progressively reduced. Because his tongue was enormously swollen, the patient was transferred to the intensive care unit while sedated, and his trachea was extubated 6 hours later. At this time, our hypothesis was that contrast media Hexabrix® may have caused the anaphylactic reaction. The patient was referred to the Allergy and Immunology Clinic, and a complete workup was done 2 months later (Table 1). A type I allergic reaction to chlorhexidine and a nonspecific reaction to propofol were diagnosed. At this time, we were not aware that either chlorhexidine or propofol had been used, and the immunologist suspected the contrast media to have caused the reaction by nonspecific histamine liberation.

Three months later, the patient was rescheduled for the same procedure (second procedure). Because we could not identify the exact agent causing the earlier anaphylactic reaction, general anesthesia was instead induced with etomidate, fentanyl, vecuronium, and maintained with sevoflurane. Following the recommendations of the immunologist, we administered antihistamines (clemastine 2 mg IV and ranitidine 50 mg IV) and hydrocortisone (250 mg IV) as premedication for anesthesia. Antibiotic prophylaxis was done using cefuroxime 1.5 g IV. As in the previous procedure, the patient remained hemodynamically stable until the beginning of surgery. However, just after starting cystoscopy, the patient developed severe bronchospasm, progressive swelling of the tongue, and severe hypotension. Again, the operation had to be aborted notably before administering any contrast media. The patient was transferred to the intensive care unit, and the epinephrine infusion with rates as high as 30 mcg·min⁻¹ was stopped 6 hours later. There was generalized erythema, a massive capillary leakage (hemoglobin 18.4·g·L⁻¹), severe intraoral, and urethral mucosal swelling, and the trachea remained intubated until the following day. The patient was again referred to the Allergy

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Table 1. Immunological Workup

	Potential allergens	Workup
First procedure	Anesthetics Midazolam, thiopental, fentanyl, rocuronium, sevoflurane Antibiotics Amoxicillin/clavulanic acid Disinfectants Povidone-iodine Others Contrast media (iodine containing), latex, lubricants	Perioperative Chart review, serum tryptase not measured Allergy and immunology clinic 2 months after the 1st procedure Skin testing (prick, scratch, and intracutaneous tests) Multiple anesthetics (including those administered): negative, except mild reaction to propofol (mild erythema and pruritus on 1:1000 diluted propofol intracutaneously) Multiple antibiotics (including amoxicillin/clavulanic acid): negative Multiple disinfectants: negative, except chlorhexidine Multiple contrast media: negative Latex: negative Total and specific IgE antibodies Total IgE in normal range ($<100 \text{ kU}\cdot\text{L}^{-1}$) Specific IgE positive to chlorhexidine ($6.1 \text{ kU}\cdot\text{L}^{-1}$), negative to amoxicillin, penicillin G and V, latex Serum tryptase in normal range ($1.16 \text{ mcg}\cdot\text{L}^{-1}$)
Second procedure	Premedication Clemastine, ranitidine, hydrocortisone Anesthetics Etomidate, fentanyl, vecuronium, sevoflurane Antibiotics Cefuroxime Disinfectants Povidone-iodine Others Latex, lubricants	Perioperative Chart review, serum tryptase not measured Allergy and Immunology Clinic 2 months after the 2nd procedure Skin testing (prick, scratch, and intracutaneous tests) Multiple anesthetics (including those administered): negative, except mild reaction to propofol (mild erythema and pruritus on 1:1000 diluted propofol intracutaneously) Multiple antibiotics (including cefuroxime): negative Total and specific IgE antibodies Total IgE in normal range ($<100 \text{ kU}\cdot\text{L}^{-1}$) Specific IgE positive to chlorhexidine ($5.7 \text{ kU}\cdot\text{L}^{-1}$), negative to amoxicillin, penicillin G and V, latex Lymphocyte transformation test Positive to amoxicillin (mild proliferation) Basophil activation test (Flow2CAST) Positive to cefuroxime and benzyl-penicillin (mild activation)

and Immunology Clinic 2 months later (Table 1). In addition to confirming the previous findings (type I allergic reaction to chlorhexidine and unspecific reaction to propofol), further sophisticated testing to antibiotics was done, and some antibiotics tested mildly positive (lymphocyte transformation and basophil activation tests; Table 1). Therefore, despite negative skin tests, we concluded that the antibiotics, although unlikely, may have caused the anaphylaxis.

Three months later, the patient presented for removal of the large kidney stone that had remained in place for >6 months. In preparation for the anesthesia, we found several reports on severe anaphylaxis to lubricants containing chlorhexidine in urological procedures.^{1,4–8} Reviewing the patient record and speaking with the urologist, it was clear that our patient received a lubricant containing chlorhexidine (i.e., Instillagel®, Endosgel®). General anesthesia was now induced and maintained with the same precautions as last time. This time, however, a lubricant without any additives was used (Lubricano®, Farco-Pharma, Germany), and the patient remained hemodynamically stable throughout the case. Since the patient developed a severe stricture of the urethra during the second procedure, he required anesthesia for reconstructive surgery 4 months later that was completely uneventful.

DISCUSSION

Chlorhexidine is a widely used disinfectant and antiseptic agent in medical and nonmedical environments. Since its

increasing use, allergic reactions to chlorhexidine, from contact dermatitis to severe anaphylaxis, have been described over the last few years.^{4,8–12} Anaphylactic reactions to chlorhexidine occur more frequently when used as disinfectant for insertion of catheters (central venous or epidurals) and for urological and gynecological procedures.^{1,4,7} In addition, chlorhexidine may be present as a “hidden” bactericidal coating on central venous catheters or as in our case, as antiseptic component in urethral lubricants. Direct contact with the circulation or mucosa increases the potential to cause anaphylaxis. However, anaphylaxis triggered by disinfectants containing iodine is less frequent.³

Chlorhexidine is well known as a skin disinfectant and as an antiseptic component in mouthwash or other over the counter antiseptic pharmaceuticals. However, there is little general awareness that commonly used lubricants like Instillagel® or Endosgel® contain chlorhexidine. Furthermore, since the use of lubricants is so common for urological procedures, it is rarely noted on either surgical or anesthesia records, as was the case in our patient. From the first immunologic workup, we were aware of the patient’s chlorhexidine allergy. Although a connection could and should have been made, none of the involved parties (anesthesiologist, urologist, intensivist, and immunologist) made the diagnosis after the first procedure.

To readily diagnose anaphylaxis can be difficult under general anesthesia because hypotension is a common side effect of many drugs administered intraoperatively, and

erythema may not be seen under the patients' drapes. For best patient outcome, however, treatment of anaphylaxis must be immediate and aggressive. In a retrospective study conducted in Denmark, the median time from first signs of anaphylactic shock to treatment was 10 minutes.² After the airway is secured and all causative agents are removed, IV epinephrine (recommended doses of 0.01–0.05 mg) in combination with fluid resuscitation are considered first-line therapy. Histamine-blocking drugs and steroids should be given secondarily.¹ For further workup, blood sampling should be done as soon as possible (without delaying patients' resuscitation) and serum tryptase measured in a first, second (after 1–2 hours), and third blood sample (after 24 hours) to estimate mast cell activation (to support the diagnosis of IgE-mediated anaphylaxis).¹ We did not obtain these early blood samples to measure serum tryptase, because our laboratory does not measure serum tryptase. Skin and further testing may follow weeks after the anaphylaxis, and a positive test must always be linked to the clinical event. Because many different agents are used in the perioperative period, it is always important to investigate all potential (including hidden) agents that might have caused the anaphylactic reactions.^{2,11} ■■

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