Case report

Sustained intraoperative allergic reaction to chlorhexidine: A case report

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Physicians should be prepared for the presentation and treatment of an anaphylactic reaction in a patient who has been exposed to chlorhexidine perioperatively and consider a sustained source of allergic exposure when faced with a refractory response to treatment. (J Allergy Clin Immunol Global 2024;3:100201.)

Key words: *Allergy, anaphylaxis, drug reaction*

Abbreviations used
BP: Blood pressure
ICU: Intensive care unit
MAP: Mean arterial pressure

Hypersensitivity to chlorhexidine is rare, especially considering the extent of its use as an antiseptic.[1,2] Cases of anaphylaxis secondary to chlorhexidine exposure are more prevalent in gynecologic and urologic procedures on account of mucosal, venous, or arterial exposure, although there are cases of topical exposure inducing anaphylaxis.[2-4] Patients typically respond to an initial treatment dose of epinephrine and removal of the offending agent. A protracted anaphylactic response is associated with increased mortality and poor long-term outcomes.[5,6] Here we present a case of development of severe and refractory anaphylaxis in a 55-year-old male in response to chlorhexidine while undergoing open abdominal surgery.

This patient, who had a medical history significant for chronic pancreatitis, was referred to a hepatobiliary surgery clinic for worsening of midepigastric abdominal pain. Following appropriate evaluation, it was decided that the patient would benefit from a Whipple procedure. He self-reported previous allergies to hydromorphone, dextropropoxyphene, and erythromycin, all causing hives. He had no history of anaphylaxis.

The patient underwent standard induction with propofol, rocuronium, lidocaine, and fentanyl. A right radial arterial line and right internal jugular central line were placed. The patient received a transversus abdominus plane and quadratus lumborum block with liposomal bupivacaine for postoperative pain control.

The patient was prepared for an open abdominal surgical procedure per hospital protocol. Chlorhexidine gluconate (ChloraPrep, Becton Dickinson, Franklin Lakes, NJ) was applied to the trunk abdomen, as well as the neck before placement of an internal jugular central line. He developed nonerythematous confluent urticaria on his trunk, abdomen, and pelvis 40 minutes after induction and within several minutes of ChloraPrep application, with stable hemodynamics. Intravenous diphenhydramine, intramuscular epinephrine, and intravenous dexamethasone were administered. He had no wheezing on auscultation, with normal peak airway pressures. As the patient was hemodynamically stable, it was decided to proceed with surgery.

An initial open incision was made without event; however, when the surgical team began to manipulate the small bowel, the patient quickly became hypotensive (with a mean arterial pressure [MAP] of 59). His hypotension was suspected to be caused by compression of the inferior vena cava. The patient's blood pressure normalized once small bowel manipulation ceased and norepinephrine was administered (58 minutes after induction his MAP was 75). The surgeons continued to manipulate the bowels and mesenteries, which were placed on the skin of the abdomen. At 61 minutes after induction, the patient's MAP was 63 despite receiving boluses of norepinephrine, vasopressin, and epinephrine. His MAP suddenly dropped to 42, requiring additional epinephrine, vasopressin, and norepinephrine boluses. Despite the decrease in MAP, the patient's heart rate ranged from 62 to 82 from the time of the initial blood pressure reading.

Norepinephrine, epinephrine, and vasopressin infusions were initiated with concomitant norepinephrine and epinephrine boluses. The patient's abdomen remained covered in ChloraPrep, with his bowels resting on his abdomen. His hemodynamic status was refractory to numerous boluses of vasopressors, and a diagnosis of shock was made, with the differential including anaphylactic or cardiogenic shock. The anesthesiologist instructed the surgery team to abort the procedure, and the surgeons promptly replaced the bowel and safely closed the abdomen. The patient's oxygen saturation declined to 82%, prompting an arterial blood gas analysis, which confirmed inadequate ventilation (Table I). His endotracheal tube was suctioned with a soft

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This study has approval from the institutional review board at Methodist Richardson Medical Center (protocol 037.HPB.2018.R). Informed consent was obtained from the patient discussed in this case report.

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TABLE I. Arterial blood gas drawn 92 minutes after induction

Arterial	Result		Normal range of values
pH	7.192	Low	7.350-7.450
pCO_2	60	High	35.0-45.0 mm Hg
pO_2	44	Low	80.0-100.0 mm Hg
HCO_3^-	23		22.0-26.0 mmol/L
Base excess	–6	Low	–2.0 to 2.0 mmol/L
Hemoglobin	12.9		13.5-17.5 g/dL

suction catheter, returning a small amount of clear mucus and no improvement in saturation.

A limited transesophageal echocardiogram was performed to assess for cardiac etiologies. It showed hyperdynamic left ventricular function with an ejection fraction of 70%, normal right ventricular size and systolic function, and no pericardial effusion. The electrocardiogram demonstrated normal sinus rhythm. A chest radiograph showed no evidence of any acute cardiopulmonary processes. The surgical team wiped the abdomen with alcohol and normal saline to remove the ChloraPrep. A presumptive diagnosis of anaphylactic shock was made. Within minutes, the patient's MAP increased to 71 and his O_2 saturation reached 99%, with the response occurring soon after the ChloraPrep had been washed from the skin.

The patient was transported to the intensive care unit while receiving epinephrine and norepinephrine infusions. He remained intubated until the following day. Physical examination in the intensive care unit showed that the urticaria and bronchospasm had resolved. He was discharged on hospital day 3 without further complications. A serum tryptase sample collected intraoperatively yielded a value of 318 ng/mL (normal value ≤10.9 ng/mL), confirming an anaphylactic response.[7]

During a follow-up interview, the patient recalled developing a rash on his hands and forearms after exposure to a chlorhexidine gluconate solution (Hibiclens, Mölnlycke Health Care, Peachtree Corners, Ga), 4.0% wt/vol, while working as a scrub technician 20 years prior. The rash resolved after he stopped using Hibiclens. Outpatient allergy skin prick testing by a trained physician-allergist returned a negative result for reaction to cefazolin and rocuronium, which are the 2 most common causes of anaphylaxis in the operating room; however, the patient did show a positive reaction to chlorhexidine. More details regarding the skin testing, including concentrations and solutions, are reported in Table II. These results, when combined with a markedly elevated tryptase level, support the diagnosis of anaphylaxis secondary to chlorhexidine exposure.

There are reports of anaphylaxis secondary to surgical preparatory washes; however, no case of anaphylaxis in response to topical chlorhexidine gluconate with a severe and refractory response has been reported.[1-4] This was demonstrated by inadequate response following appropriate doses of dexamethasone, diphenhydramine, and epinephrine, as well as by the fact that the patient's MAP could not be increased after multiple vasopressor infusions. In total, he required more than 10 mg of intravenous epinephrine, 4 mg of intravenous norepinephrine, and 20 units of vasopressin in the operating room. He required significantly higher doses of vasopressors than standard to treat his anaphylactic shock. Complete elimination of patient interaction with the offending agent allowed a proper response to treatment. Unique to this case, the patient's profound reaction is

TABLE II. Follow-up skin prick allergy testing results

Drug	Prick 1	Prick 2	ID 1:1,000, before/after	ID 1:100, before/after	ID 1:10, before/after	Result
Rocuronium (10 mg/mL)	Negative		8 × 7 (before); 7 × 8 (after)	8 × 8 (before); 7 × 6 (after)		Negative
Cefoxitin (1 g/vial)	Negative	Negative		9 × 8 (before); 8 × 8 (after)	5 × 5 (before); 7 × 5 (after)	Negative
Chlorhexidine (4% solution)	3+ flare	3+ flare				Positive
Saline	Negative				10 × 5 (before); 10 × 6 (after)	Negative
Histamine	3+ flare					Positive

ID, Initial dose.

hypothesized to be due to the tracking of chlorhexidine into the abdomen and placement of the bowel mesentery on the skin, allowing for direct uptake of the allergen. Only after the chlorhexidine had been wiped from the patient's abdomen and his bowels were returned to the abdominal cavity did he respond to treatment.

Although this case illustrates a severe allergic reaction to chlorhexidine gluconate, several other considerations should ideally be explored following severe drug anaphylaxis. Although unavailable for this patient, a patient's basal tryptase level would be important diagnostic information following anaphylaxis, serving as a baseline to trend tryptase if levels were to rise intraoperatively as the result of an allergic reaction[7,8] Similarly, mast cell pathologies, such as mast cell activation syndrome and mastocytosis, as well as hereditary α-tryptasemia should be investigated further, as described in previous literature, as possible etiologies that could present as idiopathic or severe anaphylaxis.[8,9] Measurement of allergen-specific IgE levels in the patient's blood after anaphylaxis could further help to determine the causative agent.[10,11] Immunoassays detecting specific IgE response to a number of common perioperative drugs, including paralytics, opioids, antibiotics, and chlorhexidine, are available, and some of them have high sensitivity and specificity.[10,11] Neuromuscular blocking agents, such as rocuronium, are among the most common causes of perioperative anaphylaxis, and anti–quaternary ammonium–specific IgE levels should ideally be measured to evaluate neuromuscular blocking agents as the primary cause.[12] Additionally, it is possible to utilize a number of other potential postoperative diagnostics, such as basophil activation tests, histamine release tests, and drug-induced lymphocyte stimulation tests, which have been described in previous literature to further investigate the underlying pathology that clinically presents as a severe allergic reaction.[10]

Although some of these tests were unavailable for use with this particular patient, the available data and subsequent discussion of his unfortunate reaction still constitute a novel and useful case for clinicians to be aware of. We hope that this case report can help to educate providers of one team's response to intraoperative anaphylaxis and serve as a foundation for how to proceed in similar scenarios in the future.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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