

Hetastarch Allergy and Positive Latex Radioallergosorbent Test in a Patient Suffering Cardiovascular Decompensation During Multiple Perioperative Periods

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The cause of sudden cardiovascular collapse in the perioperative period can be elusive. Allergy may be overlooked as a cause. When allergy is considered, latex is often suspected. Because hetastarch is frequently used in situations involving hypovolemia and hypotension, and because allergic reactions to it are rare, it may be overlooked as a possible allergen. We report a case of a

patient suffering cardiovascular decompensation during four nonconsecutive perioperative periods before it was determined that she was allergic to hetastarch. She also had a very highly positive latex radioallergosorbent test, suggesting a latex allergy.

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Anaphylaxis in the perioperative period is often not recognized as such (1). Many of the signs and symptoms of allergy are masked by the anesthetic and sterile draping. Even when an allergic reaction is suspected, the causative agent may be difficult to determine because of the exposure to multiple agents over a brief period of time. The most recently administered agent is often implicated, or all agents given are blamed. Because of its infrequent incidence of allergic reactions (2), hydroxyethyl starch (hetastarch) may be overlooked as a cause. Allergy testing may not reveal the culprit or may suggest the wrong one. The case presented highlights these issues.

Case Report

A 78-year-old woman (153 cm; 90 kg) with rheumatoid arthritis presented for right total knee replacement (TKR). Her medical history was significant for multiple orthopedic and lumbar spine procedures, hernia repairs, cesarean deliveries, and, most recent, a laparoscopic cholecystectomy. Her allergies included naproxen (nausea), codeine

(nausea and pruritus), and iodinated cholangiogram dye (cardiovascular collapse). She had a history of chronic allergic conjunctivitis for which she took cromolyn eye drops, psoriasis for which she used calcipotriene cream, and a pruritic disorder for which she used cetirizine hydrochloride. The preoperative assessment noted perioperative cardiovascular decompensations with three surgeries: spine surgery 8 yr before, TKR 6 yr before, and laparoscopic cholecystectomy 7 mo before. Only the most recent of the patient's 14 volumes of medical records were available. During the laparoscopic cholecystectomy, pulseless electrical activity occurred at the time of cholangiogram contrast injection. Cardiac enzymes and an echocardiogram were negative. Three hours after the event, her blood tryptase was 75.3 $\mu\text{g/L}$ (reference range, 1.9–13.5 $\mu\text{g/L}$) and a complement deficiency assay (measures the activation of classical complement components C1q-C9) was 26 U (negative >60 U). The patient made a rapid and full recovery. It was concluded that her event was anesthesia-related or caused by an allergy to the cholangiogram contrast. She was not referred for allergy testing.

Because of her history of perioperative hemodynamic decompensation during multiple surgical procedures, we suspected that the patient was allergic to latex products, although she denied any such history. We decided to proceed with the planned surgery under spinal anesthesia (to reduce the exposure to potential allergens), invasive intraarterial blood pressure monitoring, and a latex-free environment. The procedure was the first one of the day in the operating room.

After intraarterial monitoring was established, a spinal anesthetic was administered with plain bupivacaine 0.5%

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(15 mg) plus epinephrine 0.2 mg. Midazolam 1 mg IV was given for anxiolysis, cefazolin 1g IV was administered for 10 minutes, and a small-dose phenylephrine infusion was initiated to counteract the sympathectomy from the subarachnoid block. The patient was alert, comfortable, relaxed, and hemodynamically stable. The lower extremity pneumatic tourniquet remained inflated for 48 min at 300 mm Hg of pressure. At the time of tourniquet deflation, the patient had received 1800 mL of crystalloid IV. Her arterial blood pressure decreased to 75/32 mm Hg, at which time phenylephrine 100 μ g IV was given, and Hextend[®] (6% Hetastarch in lactated Ringer's electrolyte injection; Abbott Laboratories, North Chicago, IL) was initiated. Within 5 min of starting the colloid infusion, the patient complained of generalized pruritus and severe nausea. She began to retch and said she felt like she was going to die. Her systolic blood pressure decreased into the 50-mm Hg range and responded immediately to an epinephrine 50 μ g IV bolus. Her oxygen saturation and heart rate remained stable, her lungs were clear to auscultation, and there was no sign of hives or rash. The Hextend[®] infusion was discontinued after 150 mL was administered. Her pruritus resolved, but she continued to retch and was given dolasetron 12.5 mg IV. After completion of the surgical procedure, she was taken to the postanesthesia care unit (PACU), requiring several more IV boluses of epinephrine to maintain her arterial blood pressure. An epinephrine infusion was initiated. Shortly after admission to the PACU, she began to complain again of pruritus and severe chest pain. On survey of the scene, it was noted that Hextend was again being infused, having been started by a colleague assisting in the resuscitation. This was stopped after <50 mL was administered. An electrocardiogram revealed complete right bundle branch block. Arterial blood gases, hematocrit, electrolytes, and lactate were unremarkable. She also had developed wheezing bilaterally. Her condition improved over the next 3 h. The epinephrine infusion was weaned over 6 h. Cardiac enzymes were negative. An echocardiogram revealed concentric left ventricular hypertrophy but was otherwise unremarkable. Blood tryptase drawn 8 h after the event was 14.5 μ g/L and after 70 h was 4.8 μ g/L. A latex radioallergen sorbent test (RAST) was >100 kU/L (negative <0.35 kU/L). She was discharged from the hospital in good condition on postoperative Day 3.

The patient's entire archival was retrieved. Each incidence of cardiovascular decompensation was noted to have occurred immediately after hetastarch administration. The procedures in which she received no hetastarch were noted to be uneventful.

When she suffered her first cardiovascular collapse (November 1995), the anesthetic and surgery (a revision laminectomy and fusion from L3-S1) lasted 5 h 30 min, during which she received only crystalloids for IV fluids and remained relatively hemodynamically stable. Shortly after reaching the PACU, with her arterial blood pressure decreasing, she received Hespan[®] (6% hetastarch in 0.9% sodium chloride; DuPont, Wilmington, DE), 10 min after which her arterial blood pressure decreased to 61/33 mm Hg, and she rapidly deteriorated into cardiac arrest. The patient subsequently underwent four anesthetics over 19 mo without suffering cardiovascular decompensation, including an occasion in which she received hetastarch. Nineteen days after the first event, the patient underwent an incision and drainage of her lumbar wound under general endotracheal anesthesia. The intraoperative and postoperative course was essentially uneventful. In the PACU, she was

oliguric and received two 500-mL boluses of Hespan[®] without severe sequelae. However, after the initiation of the first bolus, her arterial blood pressure decreased slightly (from 105/60 to 94/60 mm Hg). After initiation of the second bolus an hour later, arterial blood pressure again decreased transiently (from 97/42 to 86/38 mm Hg), and she was given a single phenylephrine bolus of 100 μ g IV. Also, her respiratory rate increased (from 18 to 28 breaths/min) and oxygen requirements increased (3 to 6 L/min through an O₂ nasal cannula), resulting in the administration of an albuterol aerosol treatment.

Eleven weeks after her most recent event, she underwent allergy consultation. The allergist did not skin test for latex because of her highly positive latex RAST. Skin prick testing to 1:1 Hetastarch 6% and intradermal testing to 1:10,000, 1:1000, 1:100, 1:10, and 1:1 hetastarch 6% were all negative with positive histamine controls. The allergist felt that the patient's reactions were caused by latex anaphylaxis. The allergist counseled the patient regarding her presumed latex allergy and advised her to purchase a MedicAlert[®] bracelet, avoid latex products, and carry self-injectable epinephrine at all times. The allergist further stated that hetastarch could have caused an anaphylactoid rather than immunoglobulin (Ig)E-mediated reaction.

Discussion

This case details a clear association between hetastarch infusion and allergic reaction in this patient. It suggests caution in the reliance of *in vitro* allergy testing when determining the cause of a perioperative allergic reaction. Finally, it demonstrates the difficulty in identifying the cause of intraoperative events in the complex milieu of an anesthetic.

There is very little doubt that this patient has an allergy to hetastarch. She had what amounted to four positive direct antigen challenge tests, which is considered a "gold standard" for diagnosis of allergy. The relative nonreaction to hetastarch administration 19 days after the first event can be explained by the prolonged depletion of allergic mediators after the initial reaction because of the fact that hetastarch can be present in the circulation in trace amounts for 17–26 weeks (3). This may also explain the negative skin test results 11 weeks after the current episode; however, hetastarch allergy is usually non-IgE mediated (4), and skin testing would be expected to be negative. At the same time, it must be remembered that negative results to skin testing do not absolutely exclude an IgE-mediated reaction, because false negative results are possible (5).

It is not clear at all that this patient has an allergy to latex despite the very highly positive latex RAST. Although she has risk factors for latex allergy (multiple surgical procedures, allergic conjunctivitis, and pruritus), she has no history of it. The current anesthetic was the only one in which latex avoidance was observed. It can be assumed with certainty that the patient had been exposed to latex in all of her previous

procedures. It was not until September 30, 1997, that the United States Food and Drug Administration announced the requirement that all medical equipment containing latex products be labeled as such (6). Assuming latex exposure in the previous surgeries, the time course of the first reaction (5 hours 30 minutes after the anesthetic began) is not consistent with a latex allergy. Severe reactions usually occur shortly after parenteral or mucous membrane exposure (7). Furthermore, as indicated on the product container, Hextend® is latex-free. Pirat et al. (8) reported a latex allergy after tourniquet release during total knee arthroplasty. Whereas the current reaction did occur shortly after tourniquet deflation, the operating room environment, including the thigh tourniquet, was maintained latex-free. Also, the reaction in June 1997 (second reaction) occurred 25 minutes after tourniquet *inflation* with no latex-free precautions.

A positive latex RAST indicates sensitivity to latex. A patient can be sensitized and not manifest a clinical reaction, even if there is further exposure to latex (7). It is feasible that the latex RAST result was a false positive because of cross-reactivity between a latex antibody and the hetastarch molecule. Cross-reactive carbohydrate determinants have been found to be the cause of false positive *in vitro* test responses for specific IgE; however, they have not been shown to have biological activity (9,10). Skin testing for latex may have been helpful in this patient to sort out the confusion caused by the positive latex RAST. The abundant clinical information (no allergic response in the absence of hetastarch administration) would have made this test highly sensitive, unless trace amounts of hetastarch caused prolonged mediator depletion.

This case highlights the difficulty in diagnosing allergy in the perioperative period. The differential diagnosis of cardiovascular decompensation under anesthesia is broad. Even when clinicians suspect a reaction to the anesthesia, allergy may not be specifically considered. In the first reaction, it was easy to see how allergy was overlooked because of immediate concerns of hypotension secondary to hypovolemia. The deterioration of the patient after hetastarch administration was certainly viewed by the clinicians as sequelae of the hypotension (myocardial ischemia). In the second reaction (TKR under spinal anesthesia), it was obvious that allergy was never considered, although the patient was stable until hetastarch was administered. Unfortunately, this is not an unusual situation. Jacobsen et al. (1), using a full-scale patient simulator, demonstrated that clinicians often fail to diagnose allergic reaction; instead, they frequently attribute the signs and symptoms to light anesthesia or hypovolemia from

hemorrhage. It was not until the third episode (laparoscopic cholecystectomy; March, 2003) that an allergic reaction was seriously entertained. Despite the fact that hetastarch had been initiated shortly before the reaction, it was never considered as a possible allergen; it was assumed that the cholangiogram contrast agent was the proximate cause. Although an allergy was diagnosed by history, physical examination, and laboratory data, the patient was never referred for allergy evaluation, possibly because the contrast agent was presumed to be the definite cause. Even if the patient had had formal allergy testing at that time, it is unlikely that she would have been tested for hetastarch because it was not suspected (it is an unusual cause of allergy). If she was tested for hetastarch allergy, the skin tests would likely have been negative. If a latex RAST was performed, and it was positive, latex avoidance would have been advised. This information would not have helped her for the current case because latex avoidance was already planned.

We conclude that determining the cause of cardiovascular decompensation in the perioperative period can be difficult. Physicians should be alert to the possibility of allergic reaction. Likewise, when hetastarch is given, it should be included in the differential diagnosis of allergic reaction. When an allergic reaction is suspected, immediate consultation with an allergist is recommended to help with treatment and diagnosis. *In vitro* tests that may confirm the suspicion of allergy include serum tryptase, serum histamine (drawn immediately after a reaction), 24-hour urine histamine, and RAST (11). A detailed history and thorough review of the records and timing of administration of medications and colloids may give clues to the possible allergen. Comprehensive allergy testing (skin testing and graded challenge tests) performed 4–6 weeks after a reaction is mandatory (11) but may not yield a satisfactory result.

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