9. Mason JE, Stinson EB, Harrison DEC: Autonomic nervous system and arrhythmias studies in the transplanted denervated human heart. Cardiology 61:75–80, 1976

10. Pope SE, Stinson EB, Daughters GT, Schroeder JS, Ingels NB, Alderman EL: Exercise response of the denervated heart in long-term cardiac transplant recipients. Am J Cardiol 46:213–218, 1980

11. Kavanagh T, Yacoub MH, Mertens DJ, Kennedy J, Campbell RB, Sawyer P: Cardiorespiratory responses to exercise training after orthotopic cardiac transplantation. Circulation 77:162–171, 1988

12. Fallen EL, Kamath MV, Ghista DN, Fitchett D: Spectral analysis of heart rate variability following heart transplantation: Evidence for functional reinnervation. J Auton Nerv Syst 23:199–206, 1988

13. Stark RP, McGinn AL, Wilson RF: Chest pain in cardiac-transplant recipients. N Engl J Med 324:1791–1794, 1991

14. Kuffler SW, Dennis MJ, Harris AJ: The development of chemosensitivity in extrasynaptic areas of the neuronal surface after denervation of parasympathetic ganglion cells in the heart of the frog. Proc R Soc Lond [Biol] 177:555–563, 1971

15. Kaseda S, Zipes DP: Supersensitivity to acetylcholine of canine sinus and AV nodes after parasympathetic denervation. Am J Physiol 255:H534–H539, 1988

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Anaphylactic Reaction to Topical Bovine Thrombin

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THE use of topical bovine thrombin (TBT) alone or in conjunction with cryoprecipitated fibrinogen is common for facilitation of intraoperative hemostasis for a variety of surgical procedures.[1–4] Topical bovine thrombin may be applied directly, or in conjunction with surgical sponges or gelatin sponges, to bleeding capillaries or small venules, and acts specifically by clotting fibrinogen in the blood. The speed with which a clot forms is dependent on the concentration of the solution used and the serum level of fibrinogen. Topical bovine thrombin is a protein substance with a high antigenic potential that may lead to the development of antithrombin antibodies and, although relatively rare, anaphylactoid reactions to TBT may, therefore, occur on reexposure to the drug.‡[5,6] The severity of this or any other anaphylactic reaction may be mediated by the concomitant administration of β-adrenergic antagonists, with these agents not only impairing the efficacy of epinephrine in treating the condition, but also altering the threshold for pronounced anaphylaxis.[7]

In this report, we describe a patient in whom anaphylaxis occurred immediately after the application of TBT, and whose initial therapy was hampered by the prior administration of a β-adrenergic antagonist.

Case Report

A 51-yr-old man with a history of lumbar stenosis was admitted for treatment of decompressive lumbar laminectomy and spinal fusion. The patient's past surgical history was remarkable for uncomplicated cervical spine fusion 5 yr before admission, and a lumbar root decompression 2 yr before admission. The patient's past medical history was otherwise unremarkable. He denied prior transfusion therapy. He denied tobacco or alcohol abuse and the only medication he was taking was aspirin. His allergy history was remarkable for sulfa-induced skin rashes. He denied other manifestations, such as urticaria, stridor, bronchospasm, or shock. His physical examination was remarkable only for a positive straight leg raise sign bilaterally. Preoperative laboratory values were within normal limits, with the exception of a cholesterol of 228 mg% and an alkaline phosphatase of 133 μL (normal 35–110 μL). Chest x-ray and electrocardiogram were also within normal limits.

The patient received no preoperative medication the morning of surgery. Before the induction of anesthesia, two 16-g peripheral intravenous lines and a 20-g radial arterial catheter were inserted under local anesthesia with lidocaine 1% subcutaneously. A total of 3 mg of midazolam was titrated intravenously for preoperative sedation. Cefazolin, 2 g in 100 ml of 0.9% normal saline, was infused over 20 min for surgical prophylaxis. Routine monitors were placed and the patient breathed oxygen. Anesthetic induction with thiopental, sufentanil, and vecuronium ensued and was followed by uncomplicated tracheal intubation. Electrodes were placed at the posterior tibial nerves and the scalp for somatosensory evoked potential monitoring (SSEP). The patient was then placed in the prone position using an Andrew's frame. The patient's vital signs remained stable while he received 70% nitrous oxide and a sufentanil infusion of 0.3

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‡ Usuda T, Shiroyama Y, Tanaka E, Matsuda T, Yokoo K, Hiramatsu M, Izawa Y: A case report of anaphylactic shock caused by thrombin topical. Jap J Burn Injuries 12:55–59, 1986.

$\mu g \cdot kg^{-1} \cdot h^{-1}$. Before surgical incision, deliberate hypotension was induced with isoflurane, 0.2–0.3% (end-tidal concentrations), and intermittent doses of labetalol (20 mg total over 2 h) to maintain a mean arterial pressure between 55 and 65 mmHg. Surgery proceeded for approximately 2 h without complication. Blood loss was estimated to be 250–300 ml. During this period, the patient received 2000 ml of Ringer's lactate solution and 500 ml of hydroxyethyl starch. The intraoperative hematocrit was 38%.

On completion of the decompressive laminectomy and before the anticipated spinal fusion, surgical gelatin sponges soaked with topical bovine thrombin (Thrombin, USP; Thrombostat, Parke-Davis, Morris Plains, NJ) were placed at the iliac bone graft site to improve hemostasis. Within 2–3 min after the application of TBT, the patient developed profound bradycardia (heart rate 30–35/min) and hypotension (mean arterial pressure 20–30 mmHg). Isoflurane, N_2O, and sufentanil were discontinued and 100% oxygen was administered. Atropine 1.0 mg intravenous and ephedrine 50 mg intravenous were given with minimal effect. An additional 1 L of Ringer's lactate and epinephrine 0.5 mg intravenous improved the mean arterial pressure to 50 mmHg. The electrocardiogram now revealed sinus tachycardia with 3–4 mm ST segment depression. Breath sounds were clear and no urticaria was detected on the arms or back. Surgical closure was completed (aborting an attempt at spinal fusion) and the patient was turned to the supine position. The resuscitative effort lasted 20 min. In the supine position, the patient's blood pressure returned to a mean pressure of 90 mmHg, although he remained slightly tachycardiac. The SSEP signal remained unchanged (P_1 = 48 msec). The ST segment depression resolved and the patient awoke moving all extremities and following commands. The initial arterial blood gas on 100% Fi_{O_2} and the patient breathing spontaneously had a pH of 7.26, p_{CO_2} of 56 mmHg, and p_{O_2} of 449 mmHg. The hemoglobin was 11.9 g% and the serum sodium, calcium, potassium, and glucose were all within normal limits. Neostigmine 5 mg and glycopyrrolate 1.0 mg were given to fully reverse the effects of the muscle relaxant and the patient was transferred to the postanesthesia care unit (PACU).

In the PACU, hypotension and tachycardia returned and persisted despite 1 unit of autologous whole blood and 500 ml of Ringer's lactate. A pulmonary artery catheter was inserted and revealed a pulmonary artery occlusion pressure of 1 mmHg. Cardiac output was 9.82 L/min and calculated systemic vascular resistance was 578 $dyne \cdot s \cdot cm^{-5}$ consistent with anaphylaxis as the cause of hypotension. On further physical examination, diffuse urticaria was noted solely in the periumbilical and anterior thigh regions, areas initially nonvisible while the patient was in the prone position.

Hydrocortisone, 100 mg intravenous; diphenhydramine, 50 mg intravenous; and famotidine, 20 mg intravenous, were administered and the patient's condition rapidly stabilized. The trachea was extubated without complication.

Because of the temporal relationship between the administration of TBT and hypotension, immunologic studies were ordered. A serum tryptase level on a blood sample obtained in the PACU (approximately 2 h after the initial episode of hypotension) was 6.7 ng/ml (nl < 1 ng/ml). Five days later, the patient was evaluated with IgE-skin testing. A panel of common aeroallergens, beef extract, and concentrations ranging from 0.1 U/ml to 1,000 U/ml of TBT (diluted in sterile 0.9% NaCl) were tested using the puncture method. All tests were negative, although the positive histamine control gave a 12 × 15-mm wheal. The patient's recovery was otherwise uneventful. Myocardial infarction was ruled out, and a persantine thallium study showed no evidence of coronary artery disease. The patient was discharged on the ninth postoperative day. Four weeks later, the skin tests were repeated. On this occasion, TBT (at 10 U/ml) produced a 6 × 6-mm wheal with a 9 × 10-mm area of erythema. Tree mix, grass mix, ragweed, whole milk, beef, and latex extracts were applied at the same time as the TBT, and none of these extracts produced a positive skin test.

Discussion

Anaphylactic reactions to thrombin-containing preparations, although rare in humans, have been described in the medical literature. In 1989, Milde reported a case of anaphylaxis to fibrin glue (cryoprecipitated fibrinogen in combination with thrombin–calcium chloride), a substance used to improve hemostasis or to seal air leaks resulting from lung lacerations or bronchopleural fistulae.[8] This patient proved to have an IgA deficiency and developed the anaphylactic reaction because of high levels of anti-IgA antibodies, rather actual anti-thrombin antibodies. Berguer *et al.* subsequently described two cases of shock that were probably secondary to direct intravascular absorption of fibrin glue during hepatic surgery.[9] Their conclusion was supported by presumptive evidence in a single dog experimental model and the lack of antibody formation in either of the patients reported.

As with these clinical studies involving fibrin glue, severe reactions to TBT have rarely been reported. However, Usada, in 1986,‡ and Sasaki, in 1990,[5] both described cases of anaphylactic shock following TBT. In the latter case, a 55-yr-old man developed shock after receiving bladder irrigation with thrombin solution for transurethral coagulation of a bladder carcinoma. This patient was also included in a prospective study by Tadokoro *et al.*, in which two additional cases of TBT-induced anaphylactic shock occurred in Japan between 1986 and 1989.[6]

Sera from these three patients revealed an increased anti-TBT percent as measured by a radioallergosorbent test (RAST), and suggested that the reaction was mediated by anti-TBT IgE antibodies. In addition, these investigators showed the value of the skin-prick test to be predictive of the presence of these IgE antibodies, much in the same fashion as we found in this patient.

Prior sensitization seems to be an important component to developing true IgE-mediated anaphylaxis.[10] In two of the three cases in the Japanese study, prior sensitization apparently occurred during previous surgeries. It is also conceivable that food allergies to beef or cow's milk may predispose a patient to react to TBT, although our patient had skin tests that were negative

to beef or whole milk. Prior sensitization to TBT has also been implicated in the development of IgG or IgM antibodies to thrombin causing a prolonged thrombin time.[11] In each of the four cases reported, the patients had been treated with TBT during previous surgery and were noted to have prolonged thrombin times without overt coagulapathies. However, when human thrombin was substituted for bovine thrombin in the assay, the thrombin time was no longer prolonged. Although the authors suggested that a patient with such antithrombin antibodies might be predisposed to hypersensitivity reactions on reexposure to TBT, it is unlikely that true anaphylaxis would occur in the absence of anti-IgE antibodies.

Our patient was probably sensitized to TBT during one of his two prior surgeries, with reexposure during this procedure yielding overt anaphylaxis. Clinically, the diagnosis was suspected with profound hypotension, urticaria, elevated cardiac output, diminished systemic vascular resistance, and a low pulmonary artery occlusion pressure.[12] Markedly elevated serum tryptase level provided evidence of mast cell activation and degranulation consistent with systemic anaphylaxis.[13,14] Serum tryptase values > 5 ng/ml are consistent with an intensity of mast cell activation sufficient to be associated with hypotension. Although mast cells can be activated by non-IgE mediated events, the positive skin test with TBT suggested that the anaphylactic episode was IgE-mediated.

Skin testing was performed using a new bottle of TBT with the same lot number as the preparation used during surgery. To avoid the possibility of a false-positive skin test because of Phemerol, which is used as a preservative in the diluent provided by the TBT manufacturer, the TBT was diluted in filter-sterilized isotonic saline.

The initial skin tests to TBT were negative with positive results 4 weeks after the anaphylactic episode. This apparent refractory period has been described for penicillin and insect venom-induced anaphylaxis.[15] Patients are usually skin-test negative for 2–4 weeks after an episode of anaphylaxis resulting from penicillin or an insect sting.

Other antigenic stimuli were suspected, including delayed reactions to the cephalosporin, thiopental, vecuronium bromide, or hydroxylethyl starch.[12] However, these stimuli were discounted based on the results of the immunologic studies. In regard to the patient's clinical course, timely diagnosis and management were initially delayed, primarily because of the patient's prone position and the nature of the anesthetic technique. The urticarial lesions were only seen in the dependent areas; solely at the lower abdomen and pelvic regions, perhaps related to the proximity of TBT in the iliac crest. The prone position in the Andrew's frame also diminished venous return and impaired adequate resuscitation during the acute anaphylactic phase. Such anesthetic agents as sufentanil and isoflurane contributed to both a diminished venous return and arterial vasodilatation, respectively, and severely prolonged the resuscitative effort.

Finally, the use of labetalol in this patient may have contributed to not only a heightened anaphylactic response to TBT, but also to a diminished effect of the β-adrenergic agonists used to restore perfusion pressure. It has been demonstrated that the production of mediators that influence anaphylaxis are controlled by neurohumoral mechanisms acting *via* cyclic nucleotides.[16] β-Adrenergic antagonists, such as labetalol, cause an increase in synthesis and release of these mediators, as well as an increase in end-organ responsiveness, by decreasing intracellular levels of cyclic adenosine monophosphate.[17] Elevated levels of antibodies have also been described in patients treated with β-adrenergic antagonists, thereby leading to more severe anaphylactic reactions.[18] In regard to therapeutic interventions for anaphylaxis, β-adrenergic antagonists block the β-1 and β-2 effects of such drugs as epinephrine, and may, therefore, favor unopposed α-adrenergic stimulation and associated bradycardia and bronchoconstriction.[19] Although bronchoconstriction was not clinically apparent, it is possible that this reflex caused the pronounced bradycardia seen in our patient. (Although the ST-segment depression on EKG probably represented a decrease in coronary perfusion pressure resulting from profound hypotension, we considered that these changes may have been mediated by unopposed, α-adrenergic-induced coronary artery vasospasm.)

Another possible explanation for the initial bradycardia is suggested by experimental models of cardiac anaphylaxis in which histamine-stimulated release of endogenous adenosine led to atrioventricular conduction delay. The bradycardic effect was, indeed, mitigated by the adenosine antagonist theophylline in this experimental model.[20]

Despite these concerns, treating anaphylaxis in a patient receiving β-adrenergic antagonists should still include epinephrine; however, early therapy with atropine should be considered to help alleviate both bron-

chospasm and bradycardia.[7] Steroids, theophylline, and H_1-antihistamines should be included as second-line agents, although it has been suggested that H_2-antihistamines, such as famotidine, ranitidine, or cimetidine, should be excluded because of their potential for decreasing the clearance of β-adrenergic antagonists by impairing hepatic blood flow.[21] Famotidine was inappropriately administered in this case, although without any adverse effect.

In conclusion, we present a case of TBT-induced anaphylaxis during general anesthesia. The severity of the response was influenced not only by the patient's position and anesthetic agents, but also by β-adrenergic blockade. Although anaphylaxis is a rare occurrence, TBT should be used with caution and with a heightened sense of awareness of this potential complication.

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References

1. Shaffrey CI, Spotnitz WD, Shaffrey ME, Jane JA: Neurosurgical application of fibrin glue: Augmentation of dural closure in 134 patients. Neurosurgery 26:207–210, 1990

2. Jasani B, Baxter-Smith DC, Donaldson LJ, Selvam A, Sokhi GS: Topical thrombin and control of wound haematoma. Lancet 2:332–333, 1977

3. Spotnitz WD, Dalton MS, Baker JW, Nolan SP: Reduction of perioperative hemorrhage by anterior mediastinal spray application of fibrin glue during cardiac operations. Ann Thorac Surg 44:529–531, 1987

4. Kram HB, del Junco T, Clark SR, Ocampo HP, Shoemaker WC: Techniques of splenic preservation using fibrin glue. J Trauma 30: 97–101, 1990

5. Sasaki A, Hashimoto Y, Eba Y, Fudeta H, Shiozawa S, Imai Y: Anaphylactic shock following topical use of thrombin for irrigation of urinary bladder. Japanese J Anesthesiology 39:1050–1054, 1990

6. Tadokoro K, Takayuki O, Takafuji S, Nakajima K, Suzuki S, Yamamoto K, Ito K, Miyamoto T, Muranaka M: Topical thrombin-induced IgE-mediated anaphylaxis: RAST analysis and skin tests studies. J Allergy Clin Immunol 88:620–629, 1991

7. Toogood JH: Risk of anaphylaxis in patients receiving beta-blocker drugs. J Allergy Clin Immunol 81:1–5, 1988

8. Milde LN: An anaphylactic reaction to fibrin glue. Anesth Analg 69:684–686, 1989

9. Berguer R, Staerkel RL, Moore EE, Moore FA, Galloway WB, Mockus MB: Warning: Fatal reaction to the use of fibrin glue in deep hepatic wounds. Case Reports. J Trauma 31:408–411, 1991

10. Stoelting RK: Allergic reactions during anesthesia. Anesth Analg 62:341–356, 1983

11. Flaherty MJ, Henderson R, Wener MH: Iatrogenic immunization with bovine thrombin: A mechanism for prolonged thrombin times after surgery. Ann Intern Med 111:631–634, 1989

12. Levy JH: Managing sequelae in the recovery room and intensive care unit, Anaphylactic Reactions in Anesthesia and Intensive Care. Stoneham, Butterworth-Heinemann, 1992, pp 175–183

13. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T: Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. N Engl J Med 316:1622–1626, 1987

14. LaRoche D, Vergnaud MC, Sillard B, Soufarapis H, Bricard H: Biochemical markers of anaphylactoid reactions to drugs: Comparison of plasma histamine and tryptase. ANESTHESIOLOGY 75:945–949, 1991

15. Lichtenstein LM, Fauci AS: Current Therapy in Allergy, Immunology, and Rheumatology. St. Louis, Mosby Year Book, 1988, pp 71

16. Bourne HR, Lichtenstein LM, Melmon KL: Pharmacologic control of allergic histamine release in vitro: Evidence for an inhibitory role of 3', 5'-adenosine monophosphate in human leucocytes. J Immunol 108:695–705, 1972

17. Schwartz LB, Austen KF: The mast cell and mediators of immediate hypersensitivity, Immunological Diseases. Edited by Samter M, Talmage DW, Frank MM, Austen KF, Claman HN. Boston, Little, Brown, 1988, pp 157–162

18. Hovmark A, Asbrink E: Effects of a beta-receptor blocking agent (propranolol) on synthesis of IgE in vitro by peripheral blood lymphocytes from atopic patients. Allergy 36:391–396, 1981

19. Hiatt WR, Wolfel EE, Stoll S, Nies AS, Zerbe GO, Brammell HL, Horwitz LD: Beta-2 adrenergic blockade evaluated with epinephrine after placebo, atenolol, and nadolol. Clin Pharmacol Ther 37:2–6, 1985

20. Heller LF, Regal JF: Effect of adenosine on histamine release and atrioventricular conduction during guinea pig cardiac anaphylaxis. Circ Res 62:1147–1158, 1988

21. Feely J, Wilkinson GR, Wood AJJ: Reduction of liver blood flow and propranolol metabolism by cimetidine. N Engl J Med 304: 692–695, 1981