

Allergic reactions to streptokinase consistent with anaphylactic or antigen-antibody complex-mediated damage

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Streptokinase used as a thrombolytic agent may produce immunologic drug reactions. We report a second case of IgE-mediated anaphylaxis and a late reaction to streptokinase. This late reaction was consistent with an IgG-mediated antigen-antibody disease with transient renal involvement, fever, and cutaneous lesions. The second case responded to prednisone therapy. (J ALLERGY CLIN IMMUNOL 76:453-7, 1985.)

Streptokinase is used worldwide as an effective and inexpensive thrombolytic agent. It is a nonenzymatic protein (47,000 MW) produced by group C β -hemolytic streptococci. Uses for S in the United States include deep vein thrombosis,^{1,2} arterial thrombosis and embolism,³ arteriovenous cannula occlusion,^{4,*} acute coronary artery thrombosis,^{5,6} and acute renal vein thrombosis.^{7,8}

Allergic reactions to S have been reported, but the characteristics of these reactions are not well-defined with a frequency of 1.7% to 18%.^{4,7,13} A recent article reviewed allergic reactions to S and reported the first documented case of anaphylaxis to S with supportive in vitro and in vivo studies supporting an IgE-mediated mechanism.¹⁴

We present two case reports of allergic reactions to S. The first case involves anaphylaxis with hypotension immediately after S administration. The second case is that of a severe delayed reaction with multiple systemic manifestations after two doses of S. Furthermore, laboratory studies are included to support immunologic processes occurring in both patients secondary to S therapy.

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*Data file for arteriovenous cannula occlusion. Hoechst-Roussel Pharmaceuticals, Inc.

Abbreviations used

S: Streptokinase

iv: Intravenously

CASE HISTORIES

Case 1

A 72-year-old white man with a history of metastatic adenocarcinoma of the colon was admitted to Saint Elizabeth Medical Center in Granite City, Ill., for evaluation of increasing rectal pain. A central venous pressure catheter was required during his hospitalization that subsequently became clotted. S was used in an attempt to lyse the clot. The patient's vital signs preceding the S infusion were normal. Forty minutes after the patient received a dose of S iv, he was found slumped in a chair, pale in appearance, lethargic, and responded poorly to verbal stimuli. His skin was cold to the touch, and no urticaria or angioedema were present. His blood pressure was 72/60, pulse was 50, and respiratory rate was 28. The patient had been afebrile. There were no significant changes in the physical examination. He responded to intravenous epinephrine, methylprednisolone sodium succinate (Solu-Medrol; Upjohn Co., Kalamazoo, Mich.), and dopamine infusion. His medications preceding the event were continued without adverse reactions. These included aspirin (Ascriptin; William H. Rorer, Inc., Ft. Washington, Pa.), quinidine, dipyridamole (Persantine; Boehringer Ingelheim, Ridgefield, Conn.), psyllium, triazolam (Halcion; Upjohn Co.), timolol maleate (Timoptic; Merck Sharp & Dohme, West Point, Pa.), ampicillin, neomycin sulfate, erythromycin (Vivonex; Norwich-Eaton Pharmaceuticals, Norwich, N.Y.), meperidine hydrochloride (Demerol; Breon Laboratories Inc., New York, N.Y.), and diazepam (Valium; Roche Laboratories, Puerto Rico). He had no past history of hay fever, asthma, urticaria, or drug allergy, including S.

Case 2

A 64-year-old white man with a history of hypertension was transferred to Northwestern Memorial Hospital coronary care unit after two recent infusions of S. Five days earlier he had been admitted to another hospital with an acute inferior wall myocardial infarction. He had no previous history of organic heart disease. His preadmission medications included allopurinol, 300 mg by mouth every morning, hydrochlorothiazide, 50 mg by mouth every morning, and metoprolol, 100 mg by mouth twice daily. His physical examination on admission revealed a blood pressure of 174/104, pulse of 56, temperature of 95.4° F, and a respiratory rate of 24. Complete blood count with differential, platelet count, prothrombin time, partial thromboplastin time, urinalysis, blood urea nitrogen, creatinine, serum aspartate aminotransferase, serum potassium, chloride, and sodium were within normal limits. A chest radiograph revealed mild cardiomegaly with pulmonary vascular congestion. The EKG demonstrated changes consistent with an acute transmural inferior wall myocardial infarction. Thrombolytic therapy was begun 2½ hours after the onset of his chest pain. After doses of 100 mg of hydrocortisone and 3000 units of heparin iv, 750,000 IU of S was infused iv during 10 minutes. A second 750,000 IU infusion of S was administered 15 minutes after the first infusion, and a continuous infusion of heparin was begun. This dose of S was tolerated well. Cardiac isoenzymes subsequently confirmed the diagnosis of an acute myocardial infarction. Two and a half days later the patient again complained of crushing substernal chest pain, and an electrocardiogram demonstrated reelevation of the ST segments in the inferior leads. At that time it was noted that the heparin infusion had been inadvertently stopped. A second infusion of S was administered as above 1½ hours after the onset of pain. The cardiac isoenzymes did not reelevate after this episode. No immediate adverse reactions occurred; however, 4 hours later the patient was described as "shivering" with a temperature of 101.5° F (orally) and a pulse of 119. Intermittent elevations in body temperature continued for the next 3 days. An erythematous, painful skin eruption developed on the right hand and forearm 2 days after the last dose of S. This cutaneous eruption was believed to be cellulitis or phlebitis. The patient received one dose of amikacin (500 mg), and cefazolin was begun at 2 gm every 8 hours iv. The next day after transfer to our institution, high fever persisted, and the inflammation in the right arm had not improved with antibiotic therapy. The antibiotics were changed to piperacillin and amikacin. The following day routine electrolytes revealed a blood urea nitrogen of 73 and creatinine of 3.4. These had been normal, and there had been no recent hypotension. Urine output remained adequate. The urinalysis the next day was abnormal with more than 100 red blood cells per high-power field and 100 mg/dl of protein. An ultrasound of the kidneys was normal. A hippuran renal scan revealed normal perfusion to both kidneys with prolonged transit time and delayed excretion bilaterally with significant cortical retention. The erythrocyte sedimentation rate was 86 mm per hour. Fevers persisted, and cultures of blood, urine, and iv catheter tip were negative. The patient

complained of low back pain and right hip pain. A drug reaction to S was thought to be present, and prednisone, 30 mg daily, was begun and increased to 50 mg daily when new skin lesions appeared the following day characterized as painless, dark purple raised papules approximately 3 mm by 4 mm in diameter located on the right forearm and right knee.

After day 5 of prednisone therapy, the patient became afebrile, the blood urea nitrogen was 24, serum creatinine was 1.7, and the urinalysis revealed more than 100 red blood cells per high-power field and 150 mg/dl of protein.

The following laboratory results were normal or negative: immune complex screen serum complements (C₃, C₄, and CH₅₀), urine myoglobin, antinuclear antibody, rheumatoid factor, and serum cryoglobulins. Serum immune complexes were not detected by the Raji-cell technique or by Clq binding.

A skin biopsy specimen of the purple papules revealed nonspecific inflammation with some hemorrhage. Tissue immunofluorescent studies revealed no evidence of immunoglobulin (IgG, IgM, or IgA), complement (Clq, C₃, or C₄), or fibrinogen deposition in the dermis, epidermis, or dermal-epidermal junction.

Heparin therapy was continued until the patient's course was complicated by a left retroperitoneal hemorrhage requiring blood transfusions. Cardiac catheterization was performed followed by an uneventful coronary artery bypass. The patient is presently not receiving prednisone and doing well with normal blood urea nitrogen, serum creatinine, and urinalysis.

Furthermore, immunologic studies were done as outlined below on samples of the patient's serum drawn at various times throughout the clinical course. The earliest serum sample available was 2 hours after his second dose of S.

MATERIAL AND METHODS

ELISA

The ELISA assay for detection of antibody was carried out according to the methods of Voller et al.¹⁵ and Sepulveda et al.¹⁶ Briefly, the following reagents were added in sequence to Immulon micro-ELISA plates (Dynatech, Alexandria, Va.) with appropriate washes and incubation periods: S, 600 IU/ml (Streptase; Hoechst-Roussel Pharmaceuticals, Inc., Sommerville, N.J.), dilutions in duplicate of patients (case 1 and 2) and control serums (pooled serum from 10 healthy control subjects and known positive control serum from a patient who had anaphylaxis to S),¹⁵ rabbit anti-human IgG, IgE, IgM, or IgA antibody (Calbiochem-Behring Corp., La Jolla, Calif.), and alkaline phosphatase-conjugated goat anti-rabbit IgG (Sigma Chemical Co., St. Louis, Mo.). The enzyme reaction was stopped by the addition of 3M sodium hydroxide, and the optical density of each well was then read at 410 nm on a micro-ELISA mini reader MR590 (Dynatech, Santa Monica, Calif.).

Cutaneous testing

Prick and intradermal skin testing for determinations of immediate- and delayed-type hypersensitivity to S was done as previously described.¹⁴ The patient from case 1 refused skin testing. The patient from case 2 received prick test of

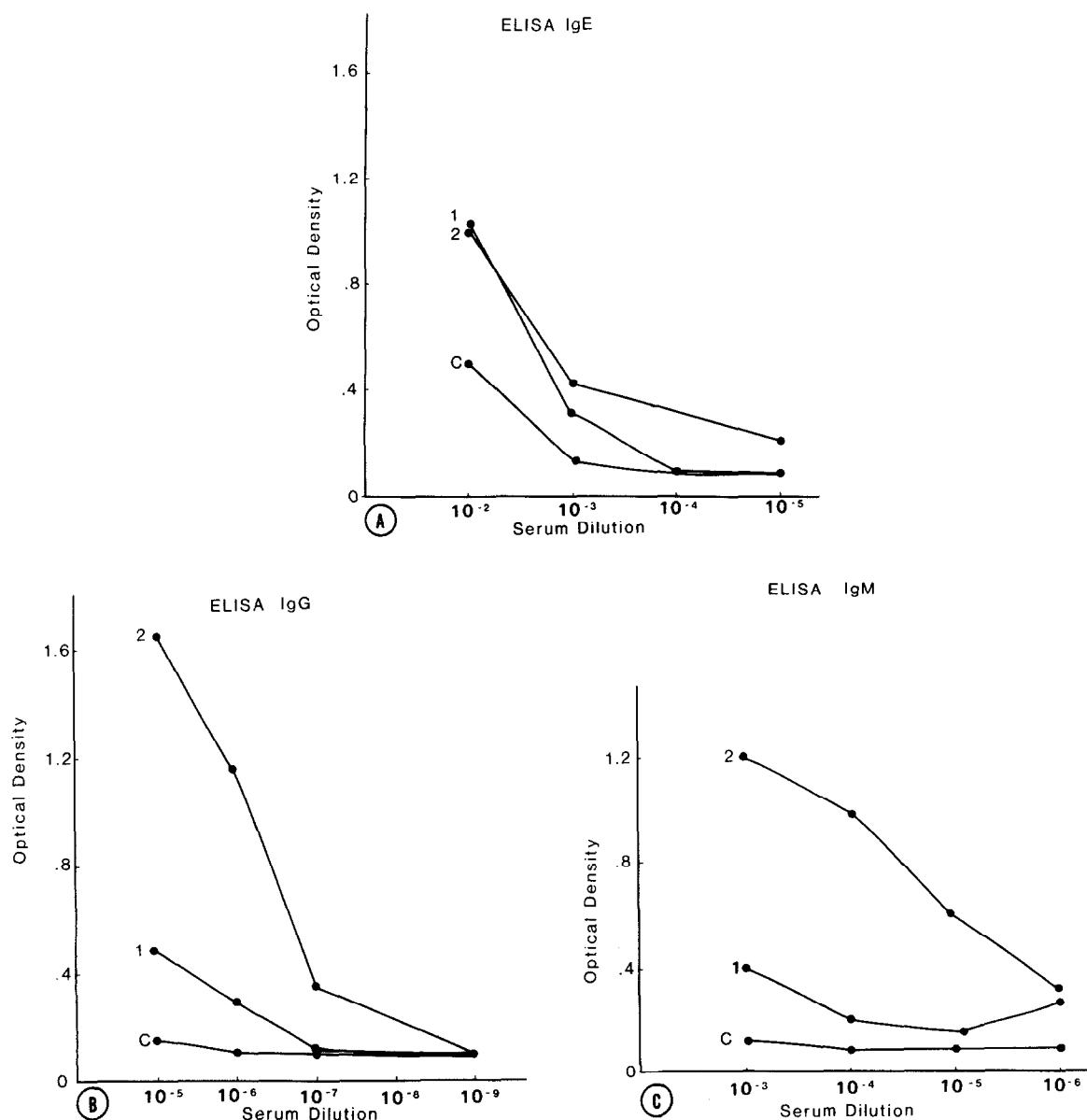


FIG. 1. A, IgE antibody to streptokinase in case 1, 2, and control (C). B, IgG antibody to streptokinase in case 1, 2, and control (C). C, IgM antibody to streptokinase in case 1, 2, and control (C).

S (Streptase) at a concentration of 300,000 IU/ml. A control of phosphate-buffered saline with 0.4% phenol was also placed. The prick skin test was read at 20 minutes. The patient received two different amounts of intradermal S, 10 IU and 3 IU, each in 0.02 ml volume with 0.02 ml of phosphate-buffered saline with 0.04% phenol as a control. A positive skin reaction was recorded if a wheal and flare occurred within 20 minutes. Measurements and drawings were made of positive reactions.

Double gel diffusion

The presence of precipitating serum antibodies in the patient from case 2 was evaluated by the double gel diffusion

technique of Ouchterlony.¹⁷ A known positive and negative control serum was included.

Lymphocyte transformation

Lymphocytes of patient 2, two positive control subjects, and one negative control subject were separated by a standard Ficoll-Hypaque method.^{18, 19} Reactivity to S was assayed by use of ³H-thymidine incorporation in a microculture technique.¹⁹ Cultures were done in triplicate and stimulated with known quantities of S. The stimulation index of the patient was compared to the stimulation indexes of the control subjects. Phytohemagglutinin-P (25 µg/ml) was included as a positive control (Difco Lab., Detroit, Mich.).

RESULTS

ELISA

In the ELISA assay the optical density at various serum dilutions is proportional to the amount of antibody present, and elevation of the optical density 1.5 to 2.0 times control at end point titrations are generally considered significant. Fig. 1, A-C, illustrate that both patients have significant demonstrable IgE, IgG, and IgM to S that were consistently greater than two times control at end point titrations. Previous ELISA inhibition studies have been carried out with S to indicate the specificity of the antibodies in this assay system.¹⁴

Skin testing

The patient from case 1 refused skin testing. The patient from case 2 had an immediate-type skin reaction with the typical wheal (4 mm by 5 mm) and flare (10 mm by 12 mm) within 5 minutes of an intradermal injection of 10 IU of S. No cutaneous reactivity occurred to 3 IU of S or to the control solution.

Double gel diffusion

Precipitating antibodies in the patient's serum of case 2 were demonstrated, forming a bond of identity with a positive control serum.

Lymphocyte transformation

Peripheral blood lymphocyte response in patient 2 to S was not elevated when response was compared to one negative and two positive control subjects. Lymphocyte reactivity was however demonstrated in patient 2 and the control subjects with nonspecific stimulation with phytohemagglutinin-P.

DISCUSSION

Allergic reactions to therapeutic use of S have been previously described; however, immunologic mechanisms have only recently been characterized.¹⁴

Case 1 represents a second study of possible clinical anaphylaxis to S supported by *in vitro* immunologic assays. This patient refused skin testing; however, IgE antibody to S by ELISA assay has previously been demonstrated to correlate to a positive immediate-type hypersensitivity skin test to S.¹⁴ It must be realized that the serum sample from this patient was drawn 2 months after the adverse reaction, and antibody levels could have developed subsequent to S exposure. Admittedly, this patient was chronically ill; however, no other cause of shock could be explained, and this, with the associated *in vitro* studies, is highly suggestive of an IgE mediated-type reaction. In a debilitated patient, shock may be the only presenting sign of anaphylaxis.

Case 2 represents a severe late-type reaction to S, possibly immune complex in origin, supported by the patient's clinical course, transient renal insufficiency, and *in vitro* studies of IgG. A lymphocyte-mediated process in patient 2 is unlikely based on the lack of lymphocyte transformation on S exposure.

The renal section of Northwestern Memorial Hospital was consulted on case 2 with a clinical impression of acute interstitial nephritis, probably drug induced. The patient had received several other potentially nephrotoxic drugs. These included three doses of amikacin, several months of hydrochlorothiazide and allopurinol therapy, cefazolin (five doses), and piperacillin (18 doses). It is unlikely that the hydrochlorothiazide or the allopurinol was the cause of the patient's renal failure because of many months of tolerance. The other drugs, including S, were, however, newly introduced and thus are more likely implicated as nephrotoxins. The short duration of amikacin, cefazolin, and piperacillin in this patient without preexisting renal disease made these drugs unlikely the nephrotoxic agents in this case. There have been two previous articles of delayed appearance of transient renal insufficiency after S therapy. These were by Totty et al.²⁰ and Staub et al.²¹ who reported two patients with a similar course to patient 2 clinically consistent with immune complex disease. Immune complexes were not detected, nor did a fall in serum complement levels occur in patient 2; however, prospective serum collections were not done because of the nature of the case.

The immunologic studies in this article further supports evidence of an IgE-mediated process in anaphylaxis secondary to S therapy in patient 1. An immune complex process may explain the delayed adverse reaction in case 2, supported by the clinical course of fever, arthralgia, skin lesions, and renal failure analogous to serum sickness and markedly elevated IgG and IgM to S by ELISA assay.

Acutely ill patients frequently receive S, and time limitations prevent *in vitro* testing to predict those at risk of S anaphylaxis or a delayed systemic reaction. Skin testing preceding S therapy is advised to predict the anaphylactic risk. We are currently preceding S therapy by an intradermal injection of 100 IU of S 15 minutes before therapy. We believe this dose will produce an immediate reaction without a large delayed reaction. If a positive immediate skin test occurs, urokinase is recommended. Repeated or continuous prolonged *iv* infusions of S had occurred in patient 2 and in the cases in the literature where an immune complex process was believed to have occurred. Skin testing with S preceding S therapy may predict those patients at risk of anaphylaxis; however, more data must be

collected. The risk of sensitization from the skin test dose of S should be of little concern when it is several times less than the therapeutic dose of S received.

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