Evidence of Anaphylaxis After Alteplase Infusion

Jobst Rudolf, MD; Martin Grond, MD; William S. Prince, PhD; Susanne Schmülling, MD; Wolf-Dieter Heiss, MD

Background and Purpose—Although alteplase, a recombinant tissue plasminogen activator (tPA), is structurally identical to endogenous tPA and therefore should not induce allergy, single cases of acute hypersensitivity reactions have been reported. Until now, specific antibodies against alteplase were not detected in blood samples obtained in these patients.

Case Description—We report an anaphylactic reaction in a 70-year-old white female who was treated with intravenous alteplase for thrombolysis of acute ischemic stroke 160 minutes after onset of a right-sided hemiparesis. Thirty minutes after infusion of alteplase had been started, the patient suffered acute severe sinus tachycardia and hypotension, followed by cyanosis and loss of consciousness. The alteplase infusion was stopped, and following antiallergic therapy, tachycardia and hypotension resolved within 1 hour. The hemiparesis remained unaltered, but additional harm resulting from the hemodynamic complication was not observed. Serum samples analyzed with a radioimmunoprecipitation assay were negative for total antibodies to alteplase, but in a subsequent ELISA, both samples were positive for IgE antibodies to alteplase.

Conclusions—The detection of specific IgE antibodies reactive with alteplase in this patient could provide the first evidence of an anaphylactic-type reaction to alteplase in man. Because previous exposure to alteplase can be excluded, the results suggest that this patient had preexisting antibodies that were cross-reactive with one or more epitopes of alteplase and therefore precipitated the anaphylactic-type reaction.

Key Words: alteplase n anaphylaxis n antibodies

Although alteplase, a recombinant tissue plasminogen activator (tPA), is structurally identical to endogenous tPA and therefore should not induce allergy, single cases of acute hypersensitivity reactions have been reported. Until now, specific antibodies against alteplase were not detected in blood samples obtained in these patients.

We report an anaphylactic reaction in a 70-year-old caucasian female who was treated with intravenous alteplase (Thomae) for thrombolysis of acute ischemic stroke 160 minutes after onset of a right-sided hemiparesis. There was no history of atopia, and except for untreated arterial hypertension, no relevant preexisting disease. Thirty minutes after infusion of alteplase had been started, the patient suffered acute severe sinus tachycardia and hypotension, followed by cyanosis and loss of consciousness. Urticarial rash, angioedema, or bronchoconstriction were not observed. There had been no previous or concurrent medication capable of inducing anaphylaxis (eg, beta-blockers). Hemodynamic collapse following supraventricular or ventricular tachycardia was excluded on the basis of 12-channel ECG recorded before the initiation of therapy and ECG monitoring during this episode. With the assumption of an anaphylactic reaction, the alteplase infusion was stopped, and the patient was treated with catecholamines and antihistamines. Tachycardia and hypotension resolved within 1 hour. The neurological deficit remained unaltered, but additional harm resulting from the hemodynamic complication was not observed. For the next 10 days that the patient spent under continuous ECG monitoring in the stroke unit, no further hemodynamic or arrhythmias were observed, and concomitant or contributory cardiac diseases were not identified.

Laboratory investigations yielded normal values for C3 and C4 complement components and proved the absence of circulating immune complexes. Serum levels of IgG, IgA, and IgM were normal, but IgE was elevated to 294 IU/mL (normal level, <80 IU/mL) on day 10 and 251 IU/mL on day 40. Additional serum samples obtained on these days were analyzed with a radioimmunoprecipitation (RIP) assay with 125I-rtPA for total antibodies to alteplase. In the RIP, both samples were negative. Anti-alteplase IgE antibodies were detected by ELISA with use of passively coated alteplase and peroxidase-conjugated goat anti-human IgE specific for the epsilon chain of immunoglobulins. As a positive control, passively coated elm pollen extract and human polyclonal IgE were used. In the ELISA, both samples were weakly positive for IgE antibodies to alteplase with logarithmic titers (minimum titer value of 1.7 required for positive reading) of 1.93 (10-day sample) and 1.81 (40-day sample). The discrep-
The discrepancy between the results of RIP and ELISA may be explained by the fact that the IgE content of human serum is only a small fraction of total immunoglobulin, and therefore even significant increases in IgE levels make only a minor difference in the overall serum antibody concentration. The RIP that determines total anti alteplase antibodies may not show a relevant increase if the IgE response is the only one generated.

This is the first report of an anaphylactic reaction to alteplase exposure that is confirmed by identification of specific IgE antibodies. The interval between start of alteplase infusion and symptom onset was within the typical range of allergic type I (anaphylactic) reactions and comparable with previous reports on similar cases, and the clinical symptoms resemble those observed by Okpara and coworkers. Even though clinically manifested atopia could not be established from the patient’s medical history, persistent elevated serum IgE levels were found. Elevated total serum IgE levels were reported from patients with history of atopia and anaphylactoid reaction to alteplase, but specific antibodies to alteplase were not detected. Therefore, the allergic etiology of anaphylactoid reactions following alteplase infusion was questioned, and a complement-mediated reaction was assumed.

Elevated levels of serum IgE are observed as a response to myocardial infarction and stroke and do not necessarily reflect an allergic reaction. However, the detection of specific IgE antibodies reactive with alteplase (anti-tPA IgE) in this patient could provide the first evidence of an anaphylactic-type reaction to alteplase in man. As previous exposure to alteplase can be excluded, the results suggest that our patient had preexisting antibodies that were cross-reactive with one or more epitopes of alteplase and therefore precipitated the anaphylactic-type reaction. Although the incidence of these anaphylactic reactions seems to be extremely rare (altogether 4 reported cases in over 1 million applications), their occurrence cannot be excluded.

References
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