

# Anaphylactoid Reaction and Angioedema after Infusion of Recombinant Tissue Plasminogen Activator

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## Abstract

An anaphylactoid reaction to recombinant tissue plasminogen activator for thrombolytic treatment of acute ischemic stroke is an uncommon complication. An increased risk of anaphylaxis may be found in patients concomitantly being treated with angiotensin-converting enzyme inhibitors (ACEI). This case report describes a patient who experienced hypotension, tachycardia, dyspnea, orolingual angioedema, and airway obstruction following intravenous administration of alteplase, although she was not taking an ACEI. Possible pharmacologic interactions resulting in excessive serum bradykinin and subsequent systemic hypersensitivity responses are discussed.

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## Introduction

Recombinant tissue-plasminogen activator (rt-PA) is the only approved pharmacological therapy for acute ischemic stroke that not only improves the prognosis of acute cerebral ischemia but also is relatively safe [1]. Adverse effects include intracerebral, gastrointestinal, genitourinary, retroperitoneal, or pericardial hemorrhage, nausea, vomiting, hypotension, and allergic reactions. Symptomatic cerebral hemorrhage, the most serious adverse event, is reported to occur in 2-9% of patients receiving intravenous (IV) rt-PA therapy. Cases of allergic reaction to IV rt-PA are very rare, reported in only 1.3-5% of patients [2], and command little attention. However, symptoms of an allergic reaction vary widely, from transient and mild oral and lingual angioedema, nausea, and hypotension to life-threatening symptoms that may require intubation or tracheostomy. rt-PA is structurally identical to intrinsic tPA, which accounts for the lower incidence of allergic reactions compared to other thrombolytics, but the risk of an allergic reaction increases in patients who are on an angiotensin-converting enzyme (ACE) inhibitor [3].

## Case Report

A 74-year-old female presented to the emergency department with right-sided weakness that started 2 hours prior. She had a past medical history of hypertension, for which she was taking amlodipine 2.5 mg. Neurological examination showed dysarthria, facial paralysis, and weakness of the limbs, and she scored 6 on the National Institutes of Health Stroke Scale (NIHSS). On presentation, her blood pressure was 156/88 mmHg, pulse rate was 106 per minute, respiratory rate was 20 per minute, platelet count was 178,000/ $\mu$ L, activated partial thromboplastin time (aPTT) was 30.8 seconds (normal range 28.0-45.0 seconds), prothrombin time (PT) was 13.0 seconds (normal range 11.6-15.5 seconds), with international normalized ratio of 1.01 (normal). Computed topography (CT) did not reveal cerebral hemorrhage or early ischemic changes, and no vascular occlusion was evident. Therefore, 0.9 mg/kg of rt-PA, totaling 50 mg, was given over 1 hour at 30 minutes after presentation and 2.5 hours after symptom onset. After the completion of rt-PA injection, the patient scored 2 on the NIHSS, and symptoms other than facial paralysis improved. Brain magnetic resonance imaging (MRI) confirmed left basal ganglia ischemia. However, 2 hours after rt-PA injection, the patient suddenly complained of dyspnea and subsequently developed decreased alertness and dysarthria. The patient's blood pressure was

94/57 mmHg, pulse rate was 78, respiratory rate was 23, and oxygen saturation was 100%. Examination did not reveal any rashes or wheezes. Normal saline dose was increased, and brain and chest CT did not reveal cerebral hemorrhage or pulmonary embolism. The patient was placed in Trendelenburg position, and colloids were added to her fluid regimen, but her blood pressure continued to decrease. The patient was diaphoretic and developed cold extremities and angioedema of the lips. Methylprednisolone 125 mg and chlorpheniramine 2 mg were administered, and hypotension as well as oral angioedema improved within 20 minutes. However, right hemiparesis and dysarthria persisted, and the NIHSS score did not improve to 5 until discharge.

## Discussion

Anaphylaxis is a severe, systemic allergic reaction. An immune reaction to an allergen produces immunoglobulin E (IgE) antibodies. When the same allergen that caused the initial immune reaction enters the body again, it binds to IgE and leads to the secretion of histamine and bradykinin, which in turn cause severe systemic reactions that resemble shock. Symptoms similar to anaphylaxis without concrete evidence of an immune basis are called anaphylactoid reactions. This patient was not previously exposed to rt-PA, and IgE antibody titer was not measured. Therefore, this case cannot be confirmed as anaphylaxis. However, the possibility of cross-reactivity with tPA epitope cannot be excluded.

Even if this case was not one of anaphylaxis, rt-PA can activate the complement system by increasing the plasma concentrations of C4a, C3a, and C5a, ultimately leading to histamine secretion from mast cells [4]. rt-PA also activates plasmin and produces bradykinin from its precursor, kininogen. Bradykinin is a vasodilator that increases vascular permeability and can cause angioedema [3]. Patients on an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II

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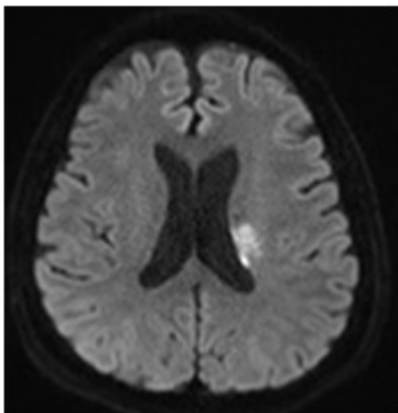


Figure 1: Left basal ganglia high signal intensity on Diffusion weighted magnetic resonance imaging.



Figure 2: No pulmonary thromboembolism on enhanced chest computed tomography.

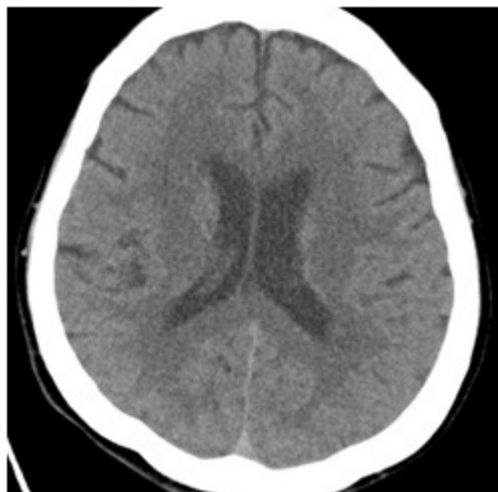


Figure 3: No hemorrhage on Brain computed tomography after rt-PA infusion.

symptoms such as hypotension, buccal angioedema, and decreased alertness, which were ameliorated with antihistamine and steroid. This can lead to the diagnosis of an anaphylactoid reaction. Anaphylactoid reactions can improve with supportive therapy alone, but may sometimes require intubation. Attention must be paid to allergic reactions to rt-PA in order to respond in a timely manner.

### Abbreviations

rt-PA: Recombinant tissue-Plasminogen Activator  
ACE: Angiotensin-Converting Enzyme  
NIHSS: National Institutes of Health Stroke Scale  
CT: Computed Tomography  
IgE: Immunoglobulin E  
ARB: Angiotensin II Receptor Blocker

### Competing Interests

The authors declare that they have no competing interests.

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receptor blocker (ARB) can be more susceptible to angioedema. This is because an ACE prevents the breakdown of bradykinin and increases its plasma concentration. Adverse events seen in patients on ACE inhibitors or ARBs, such as angioedema and cough, are also due to the increased concentration of bradykinin [5]. The patient in this case report was not on an ACE inhibitor or ARB, but she still developed