



Case Report

Life-threatening anaphylactoid shock caused by recombinant tissue plasminogen activator

Abstract

Recombinant tissue plasminogen activator (rt-PA) is currently the only approved agent for treating acute ischemic stroke. However, rt-PA may cause fatal symptomatic intracranial hemorrhage and other adverse effects like bleeding complications and allergic reactions. Patients taking angiotensin-converting enzyme (ACE) inhibitors have increased risk of allergic reactions. This report is about a patient with a history of ACE inhibitor intake who experienced life-threatening anaphylactoid shock during rt-PA administration. The relationship between rt-PA and ACE inhibitor was also discussed.

Recombinant tissue plasminogen activator (rt-PA) is currently the only approved agent for treating acute ischemic stroke [1]. However, it may cause fatal symptomatic intracranial hemorrhage (ICH) and other adverse effects like bleeding complications (gastrointestinal, genitourinary, retroperitoneal, and pericardial), nausea/vomiting, hypotension, and allergic reactions.

The incidence of rt-PA-associated allergic reactions is much lower compared with other thrombolytic agents because rt-PA is structurally identical to endogenous t-PA [2]. We report a patient with a history of angiotensin-converting enzyme (ACE) inhibitor intake who experienced life-threatening anaphylactoid shock during rt-PA administration. This report highlights that rt-PA should be used cautiously in patients taking ACE inhibitor.

A 61-year-old woman had a history of hypertension treated with ramipril (ACE inhibitor). She experienced acute onset left-sided weakness; and at the emergency department, her blood pressure was 162/96 mm Hg, pulse rate was 80 beats per minute, and Glasgow Coma Scale score was 15. Neurologic examination showed left-sided hemiparesis (Medical Research Council muscle power grading: 3) with mild dysarthria and National Institutes of Health Stroke Scale score of 5. Brain computed tomography done within 60 minutes of stroke onset showed no evidence of ICH. Hyperacute ischemic stroke was the impression, and thrombolytic therapy was indicated.

After obtaining informed consent, rt-PA was administered (0.9 mg/kg; total, 61 mg), initially as intravenous bolus 6.1 mg and later as intravenous infusion 54.9 mg over 60 minutes. However, 45 minutes after starting, the patient had sudden onset of nausea/vomiting and abdominal discomfort, with generalized cold sweating and dropped blood pressure (71/37 mm Hg). There was no obvious skin rash. The patient then lost consciousness (Glasgow Coma Scale: E2V1M5), and endotracheal tube intubation was performed. After crystalline fluid challenging, the shock status persisted; and vasopressor was given (dopamine 10 μ g/[kg min] as initial dose).

Forty-five minutes later, the patient improved. As her shock status resolved (blood pressure, 143/72 mm Hg), vasopressor was tapered. She was extubated, and her neurologic status returned to baseline (National Institutes of Health Stroke Scale: 5). The second brain computed tomography showed no evidence of intracranial lesion or hemorrhage. There was also no evidence of acute massive gastrointestinal bleeding (no fresh blood in the nasogastric tube, normal hemoglobin value, and negative stool occult blood). Cardiac enzymes and electrocardiogram also revealed normal results. There was no fever, the infection index was normal, and septic shock was not favored. The plasma immunoglobulin E level was within the reference range. The patient remained stable without any further deterioration.

The diagnosis of anaphylaxis includes 3 criteria (see [appendix](#)), and anaphylaxis is highly likely when any one is fulfilled [3]. The clinical symptoms/signs of this case report fulfills the second diagnostic criteria: reduced blood pressure and persistent gastrointestinal symptoms that occurred within minutes after exposure to rt-PA. Without serum immunoglobulin E level elevation or previous exposure history, the immediate reactions mimicking anaphylaxis are considered anaphylactoid responses. There is no brain herniation, ICH, active bleeding of other sites, electrocardiogram or cardiac enzyme change, sepsis, or toxic signs. Because the shock was transient and occurred during rt-PA administration, which improved dramatically within 1 hour, anaphylactoid shock secondary to anaphylactoid reactions caused by rt-PA therapy was the impression.

Several patients who have had allergic reactions (anaphylactoid reactions or angioedema) during rt-PA therapy are also being simultaneously treated with an ACE inhibitor [4].

Plasminogen activator is a serine protease that cleaves plasminogen to plasmin, which cleaves thrombus-bound fibrin resulting in the fibrinolytic effect that can also activate the complement cascade and kinin pathway [5]. Bradykinin is metabolized by aminopeptidase P, kinase I, and ACE, whereas ACE and aminopeptidase P are its first and second main inactivating pathways. Kininase I represents a minor pathway unless ACE is inhibited [6]. At therapeutic doses, ACE inhibitors alone usually do not cause a significant increase in bradykinin to induce anaphylactoid responses. However, when coupled with the activation of the complement cascade and kinin pathway induced by rt-PA, they may lead to anaphylactoid response [7]. Thus, when using rt-PA on patients regularly taking ACE inhibitors, special caution should be made.

Current guidelines suggest that intravenous administration of rt-PA is associated with improved outcomes for a broad spectrum of patients who are treatable within 3 hours of stroke onset [8]. However, the fatal adverse effects of rt-PA include bleeding complications and allergic reactions. According to a recent observational study conducted in Taiwan, the standard dose of 0.9 mg/kg rt-PA has higher rates of symptomatic ICH and mortality within 3 months compared with the lower-dose group [9]. This case report brings into question whether or not Chinese-Taiwanese patients regularly taking ACE inhibitors should receive rt-PA treatment when experiencing minor ischemic stroke because both ICH and anaphylactic shock are life-threatening.

Appendix A

Anaphylaxis is highly likely when any *one* of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

And at least one of the following:

- a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
 3. Reduced BP after exposure to known allergen for that patient (minutes to several hours)

(continued)

- a. Infants and children: low systolic BP (age specific) or > 30% decrease in systolic BP
- b. Adults: systolic BP of < 90 mm Hg or > 30% decrease from that person's baseline

BP indicates blood pressure.

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