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Case Report

Anaphylactic shock associated with intravenous thrombolytics: case report and an analysis from adverse event reporting system

Abstract

Adverse events including intracerebral hemorrhage and reperfusion arrhythmias are well known to occur with thrombolytic therapy. We report a case report of anaphylactic reaction directly attributable to intravenous (IV) recombinant tissue plasminogen activator and identify additional cases through review of the Food and Drug Administration Adverse Event Reporting System. A systematic review of Adverse Event Reporting System was performed for allergic adverse events occurring in conjunction with IV thrombolytics. We reviewed 924 adverse events which occurred between 2004 and 2012 that were associated with thrombolytics. We subsequently acquired detailed individual safety reports of 33 cases in which allergic events were documented. Out of the 33 reports, there were 12 cases (age range, 57–93 years) of adverse allergic reaction directly attributable to IV thrombolytics. Allergic reactions included angioedema, facial swelling, urticaria, skin rash, cutaneous hypesthesia, hypotension, anaphylactic shock, and death. Of the patients who were reported to suffer from allergic adverse events, 11 received IV alteplase and 1 received IV reteplase. Most reactions associated with IV alteplase resolved with withdrawal of medication and treatment with diphenhydramine and steroids $\pm$ epinephrine. There was 1 death directly attributable to allergic reaction in a patient who received IV reteplase for MI. Although IV alteplase is identical to endogenous tissue plasminogen activator, it appears to be the most common cause of allergic reaction among currently used thrombolytics, with or without concomitant administration of angiotensin-converting enzyme inhibitors. A greater awareness among physicians may result in prompt recognition and treatment.

Various intravenous (IV) thrombolytics including alteplase/recombinant tissue plasminogen activator (r-tPA), tenecteplase, urokinase, reteplase, and streptokinase are frequently used in the acute treatment of acute ischemic stroke, myocardial infarction (MI), pulmonary embolism, and deep vein thrombosis. Adverse events including intracerebral hemorrhage; gastrointestinal, genitourinary, retroperitoneal, and pericardial hemorrhages [1]; and reperfusion-associated events such as arrhythmias [2] are well characterized. However, allergic events secondary to thrombolytics are not well recognized or characterized. We report a case report of anaphylactic reaction directly attributable to IV r-tPA and identify additional cases through a review of the Food and Drug Administration (FDA) Adverse Event Reporting System (AERS).

A 61-year-old woman with a previous history of coronary artery disease requiring percutaneous coronary intervention, and hypertension treated with lisinopril presented with a 64-minute episode of acute-onset right facial weakness and right hemisensory loss with deficits by

National Institutes of Health Stroke Score of 4 in June 2011. After review of exclusion criteria, she was treated with standard dosing of IV r-tPA. Within 30 minutes of initiating r-tPA infusion, she developed relatively acute-onset hypotension with systolic blood pressure (BP) values reaching 44 mm Hg. Her extremities were noted to be hypoperfused with cold and clammy appearance. Intravenous r-tPA was immediately discontinued, and aggressive fluid resuscitation was initiated in addition to administration of 50 mg of IV diphenhydramine. After fluid resuscitation and antihistamine administration, the patient's systemic BP reached normotensive values ($\approx$ 120 mm Hg). There were no features such as rashes or oropharyngeal swelling noted. An emergent computed tomographic (CT) scan excluded any new intracerebral hemorrhage, and the hemoglobin value was relatively unchanged from the baseline value of 18 g/dL. No further episodes of hypotension were noted during hospitalization. The patient had received Omnipaque iodinated contrast agent as part of CT angiogram and CT perfusion 60 minutes before the hypotensive episode. However, the patient had received contrast agent as part of percutaneous coronary intervention previously without any documented adverse event. The patient was discharged without any residual neurological deficits on hospital day 3.

Two years later, the patient presented again with an episode of right-sided hemiparesis and hemisensory loss (National Institutes of Health Stroke Score of 3). The patient underwent a noncontrast CT scan. The patient was determined to be an appropriate candidate for IV r-tPA based on existing American Heart Association/American Stroke Association acute ischemic stroke guidelines [3]. Because of the previous reaction to IV r-tPA, she was pretreated with 50 mg of IV diphenhydramine and 100 mg of IV hydrocortisone. She was initially given a small test dose of 1 mL r-tPA, with no reaction for several minutes, after which standard-dosing IV r-tPA was administered. After 40 minutes of IV r-tPA infusion, she developed systemic hypotension with systolic BP values reaching 60 mm Hg. The r-tPA was discontinued, and IV fluids and a single dose of 0.1 mg of IV epinephrine were administered with modest benefit. At that point, a continuous epinephrine infusion was started at 0.02 μ g/(kg min). The patient's systemic BP reached normotensive values ($\approx$ 120 mm Hg). She remained in the hospital for 24 hours and was subsequently weaned from the epinephrine drip and was discharged without any residual neurological deficits.

To identify additional cases, we queried the US FDA AERS. The AERS is a database that contains information on adverse events and medication error reports submitted to the FDA by manufacturers and health care professionals. The database is designed to support the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products.

A systematic review of the AERS database was performed to identify allergic adverse events related to thrombolytics, including alteplase,

Table

Allergic reaction associated with IV thrombolytics: an analysis of the AERS (n = 12)

Patient	Age/ sex	Thrombolytic agent	Indication	Allergic reaction	Treatment reported	Associated medication
1	60 M	Activase (Genentech; San Francisco, CA)	AIS	Angioedema, with rash/hives, hypotension	Required intubation; resolved with IV fluids, steroids, Benadryl, & epinephrine	None
2	61 F	Activase	AIS	Anaphylactic shock	Required intubation; resolved with IV fluids, dopamine infusion	Ramipril
3	NA	Retevase (Cornerstone Therapeutics; Cary, NC)	MI	Cutaneous hyperesthesia, facial swelling, hypotension, fatal anaphylaxis	IV fluids, prednisolone, chlorpheniramine	Atenolol, aspirin, Lovenox, indomethacin, ISMN, diacetylmorphine Ramipril
4	80 M	Activase (Genentech; San Francisco, CA)	AIS	Angioedema with lip edema	40 mg IV Solu-Medrol, chlorpheniramine	Lisinopril, gemfibrozil
5	58 M	Activase	AIS	Diaphoresis, expiratory wheezing, unilateral left tongue edema	500 mg Solu-Medrol, Benadryl	Lisinopril, gemfibrozil
6	61 M	Activase	AIS	Angioedema requiring intubation	125 mg Solu-Medrol, Benadryl	Lisinopril
7	58 M	Activase	AIS	Angioedema requiring intubation	UNKNOWN	Lisinopril
8	93 F	Activase	AIS	Angioedema requiring intubation	Steroids, Benadryl, famotidine	ACE inhibitor
9	57 F	Activase	AIS	Angioedema	Steroids, Benadryl	None
10	80 F	Activase	AIS	Isolated swelling of bottom lip	Benadryl	Lisinopril
11	72 F	Activase	AIS	Urticaria of face and neck, lip swelling, desaturation	4 mg betamethasone	None
12	67 F	Pleural activase	Pleural loculation	Fever, skin rash	Unknown	Not reported

Abbreviations: M = male, F = female, AIS = acute ischemic stroke, NA = not available, ISMN = isosorbide mononitrate.

tenecteplase, urokinase, and reteplase. *Allergic reaction* was defined as any nonhemorrhagic sensitivity reaction that occurred as a direct result of administration of IV thrombolytic. We reviewed 924 adverse events associated with thrombolytics that occurred between 2004 and 2012. We subsequently acquired detailed individual safety reports of 33 cases in which allergic events were documented. Direct relationship was assumed based on temporal correlation to thrombolytic administration that could not be attributed to use of other medications.

Of the 33 reports, there were 12 cases (Table) (age range, 57–93 years) of adverse allergic reaction directly attributable to IV thrombolytics. Allergic reactions included angioedema, facial swelling, urticaria, skin rash, cutaneous hypesthesia, hypotension, anaphylactic shock, and death. Of the patients who were reported to suffer from allergic adverse events, 11 received IV alteplase and 1 received IV reteplase. Four of these patients were taking angiotensin-converting enzyme (ACE) inhibitors at the time of allergic reaction. In the remaining 21 events, the IV thrombolytics remained as a possible secondary cause of allergic reaction; but concomitantly administered medications made this relationship difficult to ascertain. Most reactions associated with IV alteplase resolved with withdrawal of medication and treatment with diphenhydramine and steroids $\pm$ epinephrine. There was 1 death directly attributable to allergic reaction in a patient who received IV reteplase for MI.

Histamine- and bradykinin-related mechanisms are implicated in the development of allergic reactions. Recombinant tissue plasminogen activator can activate the complement system by elevating the levels of C4a, C3a, and C5a, resulting in mast cell degranulation and the release of histamine [4]. Recombinant tissue plasminogen activator also generates plasmin, which cleaves bradykinin from its precursor kininogen. Bradykinin has vasodilator properties and increases vascular permeability, which can result in angioedema [5,6]. Both ACE inhibitor and angiotensin II receptor blocker medications reduce the breakdown of bradykinin by ACE and neutral endopeptidase, resulting in increased levels of bradykinin. The increased bradykinin concentration is known to contribute to the pathophysiology of ACE inhibitor-induced angio-neurotic edema and cough [7].

Allergic reactions to thrombolytics are most commonly associated with streptokinase administration; however, anaphylaxis is uncommon [8]. Streptokinase is produced from streptococcal bacteria and exhibits significant antigenicity and subsequently high circulating antibodies, which can lead to febrile illness and allergic reactions. The incidence of r-tPA-associated allergic reactions is expected to be

lower than that observed with other thrombolytic agents because r-tPA is structurally identical to endogenous t-PA [1].

Anaphylactoid reactions or angioedema has been reported to occur in less than 0.02% of patients treated with r-tPA for acute MI [9]. A higher incidence of allergic reactions (often asymmetric) has been reported with r-tPA administration in patients with acute ischemic stroke. Fayad et al [10] reported incidence of allergic reaction in 4 (1.5%) of 260 patient treated with IV alteplase for acute ischemic stroke. Similarly, of 105 patient treated over a 3-year period at a single center, 2 (1.9%) developed lingual angioedema, one of which events progressed to fatal anaphylactoid reaction [9].

If a manufacturer receives an adverse event report, as specified by regulations, it is required to send the report to FDA; and this is subsequently included in the AERS. However, reporting of adverse events and medication errors by health care professionals directly to the FDA is voluntary. The FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate the cause-effect relationship between medication and adverse events. Of the 924 reports reviewed, we excluded 912 cases in which there was insufficient evidence to implicate the thrombolytic as the primary cause of allergic reactions or there was insufficient detail to prove a causal relationship. Because of the voluntary nature of database, the FDA AERS data cannot be used to calculate the incidence of an adverse event or medication error in the US population.

Although IV alteplase is identical to endogenous tPA [11], AERS data suggest that it is the most commonly reported cause of allergic reaction among currently used thrombolytics, with or without concomitant administration of ACE inhibitor or angiotensin II receptor blocker medications. A greater awareness among physicians and other health care professionals may result in prompt recognition and treatment.

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