

Hypersensitivity reactions to recombinant tissue plasminogen activator

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ABSTRACT

Recombinant tissue plasminogen activator (rtPA) is currently the only approved thrombolytic agent for treating acute ischaemic stroke that is widely used in clinical practice. However, it may cause haemorrhage and hypersensitivity reactions. Orolingual angioedema is an infrequent, usually mild but potentially life threatening, hypersensitivity reaction to rtPA. Our understanding of the basic biology of angioedema has increased in recent years. There is growing evidence that rtPA-induced orolingual angioedema is driven mainly by bradykinin generation rather than it being an anaphylactic response. Monitoring is important because orolingual angioedema may evolve and compromise airways and a small number do have angioedema as part of systemic anaphylaxis. There are no published guidelines for treating rtPA-induced orolingual angioedema, although some evidence suggests that those refractory to standard antianaphylactic agents may resolve with bradykinin B2 receptor antagonists. It is important that responses to orolingual angioedema are proportionate and that patients are closely monitored.

INTRODUCTION

Intravenous thrombolysis is an effective treatment for acute ischaemic stroke.^{1 2} Recombinant tissue plasminogen activator (rtPA) is currently the only thrombolytic agent approved by England’s National Institute for Health and Care Excellence to treat acute ischaemic stroke.³

Fibrin, in forming clot, produces long strands of insoluble protein that are bound to platelets. Cross-linked fibrin forms a mesh over the platelet plug reinforcing the thrombus. rtPA is homologous to natural human tissue-type plasminogen activator. It binds to fibrin-rich clots and then cleaves plasminogen to form an active enzyme, plasmin, which degrades

the fibrin matrix of the clot, thereby promoting thrombolysis and reperfusion. Plasmin also activates the complement and kinin pathways leading to inflammatory cytokine upregulation, increased blood–mucosa and blood–brain barrier permeability and release of glutamate by glial cells. Therefore, if rtPA triggers a hypersensitivity reaction, it may be mediated by histamine (complement cascade), bradykinin (kinin pathway) or possibly both.^{4–6}

Hypersensitivity reactions following administration of rtPA are often thought of as anaphylactic.⁷ Anaphylaxis is typically secondary to mast cell degranulation and results in urticaria, pharyngeal or laryngeal oedema with stridor, bronchospasm with wheeze and tachypnoea, hypotension (with fluid shifts away from the circulation causing circulatory collapse) and tachycardia. Angioedema, as part of a hypersensitivity reaction, is caused by a rapid increase in localised vascular permeability of submucosal or subcutaneous capillaries and postcapillary venules with localised plasma extravasation. However, most rtPA-associated angioedema reactions are isolated and manifest without itch, urticaria or systemic involvement. They are mediated by bradykinin, which itself induces vascular permeability.

In this article, we discuss the underlying pathophysiological mechanisms and the clinical approach to the evaluation of rtPA-induced hypersensitivity reactions.

Anaphylaxis and rtPA

Anaphylaxis is defined as a severe, potentially fatal, multisystem, immediate hypersensitivity reaction caused by exposure to a stimulus at a strength that should be well tolerated by healthy individuals.⁸ The precise incidence of anaphylaxis to rtPA is unknown; the few published case reports^{6 9 10} suggest it is rare. A



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Table 1 Criteria for diagnosis of anaphylaxis**Anaphylaxis is highly likely when any one of the following three criteria are fulfilled.**

1.	Acute onset of illness with: Mucocutaneous involvement (pruritus, flushing, urticaria and angioedema) <i>and</i> one of the following: ▶ Respiratory compromise (wheezing, stridor, hypoxaemia and cyanosis). ▶ Hypotension* or end-organ damage (encephalopathy, kidney injury and so on).
2.	Two or more of the following occurring rapidly after exposure to an allergen: ▶ Mucocutaneous involvement (pruritus, flushing, urticaria and angioedema). ▶ Respiratory compromise (wheezing, stridor, hypoxaemia and cyanosis). ▶ Hypotension* or evidence of end-organ damage. ▶ Persistent gastrointestinal symptoms (pain, nausea and vomiting).
3.	Hypotension* after exposure to a known allergen (minutes to several hours).

*Hypotension in adults is regarded as systolic blood pressure of <90 mm Hg or greater than a 30% decrease in systolic blood pressure from the patient's baseline. Adapted from ref 11.

study of 105 patients with ischaemic stroke patients reported an anaphylaxis incidence up to 1.9% after rtPA.⁶ Anaphylaxis has varied clinical presentations, but respiratory compromise with bronchospasm or laryngeal and pharyngeal oedema and cardiovascular collapse are most serious, as they may be fatal or cause significant brain injury (table 1 box 1).¹¹ One prospective study reported older age, pre-existing lung disease and antihypertensive medications as associations with severe anaphylaxis.¹² These are common comorbidities in patients with ischaemic stroke. Anaphylaxis is likely to be more severe if rapid in onset and provoked by an intravenous agent.¹³ Increased plasma tryptase and urinary histamine concentrations from degranulated mast cells can aid diagnostic confirmation. These results may not be immediately available and should not delay treatment but can be measured for later reference.

Anaphylaxis results from the release of mediators by mast cells and basophils activated either by

immunoglobulin E (IgE), termed 'immunologic anaphylaxis', or by direct activation by other agents, termed 'non-immunologic anaphylaxis'.^{14–18} 'Anaphylactoid' was used to describe non-IgE-mediated anaphylaxis but is no longer a recommended term.¹⁹ rtPA results in non-IgE-mediated anaphylaxis via complement activation that then causes mast cell degranulation and the release of histamine.²⁰

Anaphylactic angioedema

Angioedema is characterised by acute, transient (resolving in hours to days), non-pitting, red or skin-coloured, well-demarcated swelling that involves deeper layers of skin or submucosa. It usually affects the face particularly the lips, tongue and periorbital areas. Pharyngeal, laryngeal and marked orolingual angioedema can lead to fatal airway obstruction. Intestinal angioedema can mimic an acute abdomen. Angioedema is not itchy but may be accompanied by a burning or tight sensation or by a dull ache in the affected area.

Angioedema with urticaria is the manifestation of anaphylaxis in over 90% of cases.¹³ About half the patients with urticaria also have angioedema. Only 40% have urticaria alone, and 10% have isolated angioedema.²¹ People with urticaria and angioedema tend to be more severely affected with involvement of other systems compared with those with isolated angioedema.^{21–23} Therefore, angioedema with urticaria should be treated as anaphylaxis, whereas a different clinical approach may be appropriate for isolated angioedema.

Bradykinin-induced angioedema

Bradykinin and its related kinins are small peptides with many biological effects, especially vascular dilatation and increased vascular permeability, both of which can lower blood pressure. Bradykinin breakdown is catalysed by ACE. Patients taking ACE inhibitors experience an increase in the half-life of bradykinin enhancing its biological activity. Bradykinin can also be produced when rtPA cleaves it from a large plasma protein called kininogen.⁴ Therefore,

Box 1 UK Resuscitation Guidelines (2008)
Emergency treatment of anaphylactic reactions

Anaphylaxis is likely when all of the following three criteria are met

- ▶ (1) Sudden onset and rapid progression of symptoms.
- ▶ (2) Life-threatening airway and/or breathing and/or circulation problems.
- ▶ (3) Skin and/or mucosal changes (flushing, urticaria and angioedema).

The following supports the diagnosis:

- ▶ Exposure to a known allergen for the patient.

Remember:

- ▶ (1) Skin or mucosal changes alone are not a sign of an anaphylactic reaction.
- ▶ (2) Skin and mucosal changes can be subtle or absent in up to 20% of reactions (some patients have only a decrease in blood pressure, ie, a circulation problem).
- ▶ (3) There can also be gastrointestinal symptoms (eg, vomiting, abdominal pain and incontinence).

patients taking ACE inhibitors who receive rtPA for acute stroke may have a surge in bradykinin levels. The biological actions of kinins are mediated through B1 and B2 receptors. B2 receptors are almost ubiquitous and non-selectively expressed in brain cells. They are rapidly overexpressed after brain infarction in mice.^{24 25} Once bound to receptors, bradykinin exerts a potent proinflammatory and pro-oedematous effect by increasing blood–mucosa and blood–brain barrier permeability, inflammatory cytokine upregulation, the release of glutamate by astrocytes and microglial activation^{4 5}

Angioedema without urticaria is termed primary angioedema.²⁶ Reported causes of primary angioedema are a deficiency of C1 esterase inhibitor, hereditary angioedema with normal C1 inhibitor level, ACE inhibitors and rtPA. Although each of these forms of angioedema is probably bradykinin mediated, the strength of the supporting evidence varies markedly.

ACE inhibitor-induced angioedema is uncommon and occurs in less than 1% of all people taking these drugs. It is, however, up to five times more common in the African-Caribbean population.²⁷ Up to 20% may be life threatening, especially when there is upper airway involvement.²⁸ ACE inhibitor-induced angioedema differs from rtPA-induced angioedema as there may not be an obvious relationship between exposure to the drug and appearance of angioedema.²⁹ Although half of ACE inhibitor-induced angioedema develops during the first week of treatment, in others it can develop years later.^{30 31} In contrast, rtPA-induced angioedema evolves during rtPA infusion or in the first two hours afterwards.³² rtPA-induced

angioedema may develop in up to 45% of patients using ACE inhibitors.⁴

rtPA-induced angioedema can be mediated by bradykinin, histamine or both

The underlying mechanisms of rtPA-associated orolingual angioedema are that, in addition to its therapeutic action, plasmin generated also activates complement and kinin pathways. If complement (C4a, C3a and C5a) is activated, mast cell degranulation may be triggered with resulting histamine release (figure 1),⁶ and these mediators may result in capillary leak, inflammatory cell recruitment and possibly progress to cardiopulmonary anaphylaxis.³³ This results in rapid evolution of orolingual angioedema associated with urticaria in almost all cases and followed up by potentially devastating hypotension, laryngeal oedema and bronchospasm over minutes (table 2).

Alongside histamine, rtPA-induced plasmin also triggers bradykinin overexpression^{4 5} (figure 1). Bradykinin may lead to blood–mucosa and blood–brain barrier leakage leading to orolingual angioedema, cerebral oedema and intracerebral haemorrhage.³⁴ In a mouse stroke model, pharmacological inhibition of the bradykinin pathway reduced the frequency of rtPA-induced intracerebral haemorrhage, cerebral oedema and infarct volume.³⁵ A large prospective study also reported a higher risk of symptomatic intracerebral haemorrhage in patients with acute ischaemic stroke who developed orolingual angioedema following rtPA.³⁶ However, this did not correlate with higher morbidity or mortality in those who developed orolingual angioedema compared with those who did not.³⁶

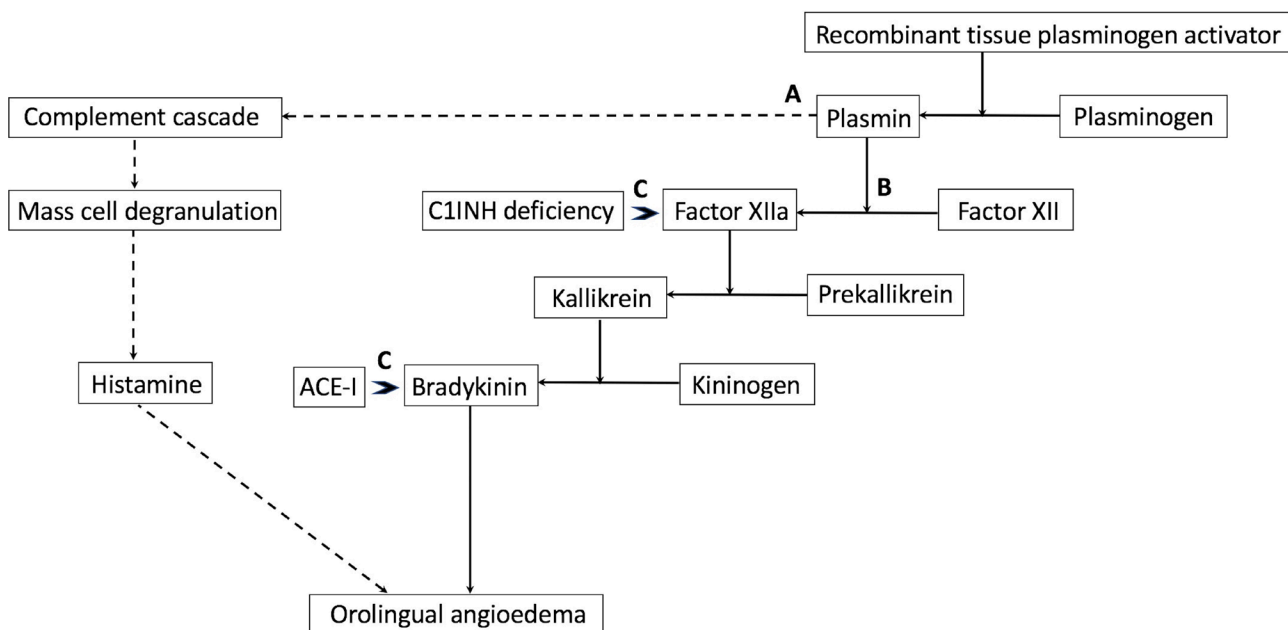


Figure 1 Mechanism of rtPA-induced orolingual angioedema. (A) (dashed lines) and (B) (solid lines) Pathways activated by rtPA indirectly via plasmin; (C) (arrowheads) factors that increase baseline bradykinin; ACE-I, ACE inhibitor; C1INH, C1 esterase inhibitor; rtPA, recombinant tissue plasminogen activator.

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Table 2 Clinical and therapeutic differences between histamine-mediated and bradykinin-mediated orolingual angioedema

Clinical features	Histamine angioedema	Bradykinin angioedema
Onset	Rapid (min)	Slow (hours)
Duration	12–24 hours	48–72 hours or more
Urticaria/pruritus	Frequent	No
Laryngeal oedema	Possible	Possible
Bronchospasm	Frequent	Rare
Hypotension	Frequent	Rare
Intracerebral haemorrhage and/or cerebral oedema	No	Possible
Treatment with H1 antihistamines, corticosteroids and epinephrine	Effective	Not effective

Adapted from ref 40.

Orolingual angioedema associated with rtPA treatment reportedly occurs in up to 7.9% patients who had a stroke.^{6 10 32 37–39} This may be an underestimate because aphasia and/or cognitive impairment may confound identification of mild orolingual angioedema. In half of cases, it develops during thrombolysis and soon afterwards in the remainder.³⁶ Orolingual angioedema usually manifests itself contralateral to the stroke, but it may be bilateral. Swelling tends to progress gradually within a few hours and may even last for several days.⁴⁰ Bronchospasm and hypotension are uncommon. While rtPA-induced orolingual angioedema is not associated with increased long-term disability, it may still be potentially life threatening.³⁶

A higher risk of rtPA-induced orolingual angioedema following acute stroke is associated with taking ACE inhibitors, insular cortex ischaemia and female sex.^{32 36–38 41 42} Patients who had a stroke taking ACE inhibitors have an increased baseline bradykinin, which facilitates the rtPA-induced bradykinin surge and orolingual angioedema, mimicking C1 esterase inhibitor deficiency.²⁶ Drug withdrawal stops or drastically reduces the risk of angioedema in most people, but it may recur in 25%.⁴³ Insular cortex ischaemia in some studies increased the risk of rtPA-induced orolingual angioedema via sympathetic activation and subsequent peripheral vasoconstriction, although not

in other studies.^{6 36 41 44} This may explain the higher frequency of rtPA-induced orolingual angioedema in people with acute stroke rather than in myocardial infarction, with a rate of 0.02%.⁶ Female sex is an independent risk factor for rtPA-induced orolingual angioedema in patients who had a stroke.^{37 41 44} Its female predominance may relate to sex hormone regulation of inflammation and women's increased immune response.^{45 46} Moreover, bradykinin-mediated hereditary angioedema attacks are more frequent just before or during menses.⁴⁷

How do we manage orolingual angioedema in patients who had a stroke?

Most hypersensitivity reactions associated with rtPA resolve on stopping the infusion. However, in the largest series reported so far, the rtPA infusion was completed in all patients suggesting a case-by-case approach is appropriate.⁷ Most cases can be managed by careful observation. In people with oral cavity or upper airway angioedema that is not critical, efforts should be made to define the site of compromise (e.g. by indirect laryngoscopy).⁴⁸ Face, mild or partial lingual, lip and soft palate oedema generally may not need intervention. Pharynx and/or larynx submucosal oedema is more worrying as airway calibre diminishes. Similarly, diffuse lingual angioedema with an inability to see the soft palate, and hoarseness or change of voice or stridor (evidence of laryngeal involvement) require immediate airway assessment (table 3). Intubation should not be delayed as swelling can progress quickly making intubation impossible and emergency tracheostomy a necessity.⁴⁹

Mild hypersensitivity reactions settle with H1 antihistamines and corticosteroid treatment. However, rtPA-induced orolingual angioedema may not resolve with standard antianaphylactic treatment^{50 51} probably due to an underlying bradykinin-driven mechanism.

Several medications approved for treating hereditary angioedema have been tested in rtPA-induced orolingual angioedema, with variable results. Icatibant is a selective bradykinin B2 receptor antagonist approved to manage hereditary angioedema in which bradykinin accumulates owing to a genetic deficiency in C1 inhibitor activity.⁵² A phase 2 randomised-controlled trial including subjects with ACE inhibitor-induced angioedema showed substantially shorter time

Table 3 Upper airway oedema classification based on severity

Stage	Clinical finding	Disposition	Airway intervention (%)
I	Facial rash, facial or lip oedema	Home or admission	0
II	Soft palate oedema	Home or admission	0
III	Lingual oedema	Intensive care unit	7
IV	Laryngeal oedema	Intensive care unit	24

Adapted from ref 48.

Box 2 Anaphylaxis management proposed protocol

- ▶ Stop recombinant tissue plasminogen activator (rtPA) infusion, lie the patient flat, elevate legs and manage the airway.
- ▶ Give adrenaline* 0.5 mg (0.5 mL) of 1 in 1000 given intramuscularly into the anterolateral thigh with prolonged compression to minimise haematoma formation post rtPA. This may be repeated.
- ▶ Consider intravenous normal (0.9%) saline 500–1000 mL fluid challenge.
- ▶ In adults, give chlorphenamine 10 mg slowly intravenously (or intramuscularly) and hydrocortisone 200 mg slowly intravenously or intramuscularly. Adrenaline is safest and most effective given intramuscularly as the intravenous route may provoke lethal arrhythmias. Early administration of intramuscular adrenaline is key to avoiding deaths in anaphylaxis. The subcutaneous route is ineffective.
- ▶ Chlorphenamine and hydrocortisone should be given slowly intravenously as further intramuscular injections increase the risk of muscle haematoma if a significant dose of rtPA has been given.
- ▶ In all patients, a mast cell tryptase should be taken as soon as possible after emergency treatment has started and a second sample ideally within 1–2 hours (but no later than 4 hours) from the onset of symptoms to help confirm the diagnosis later.
- ▶ Adapted from ref 56; Of note, adrenaline* may decrease cerebral capillary blood flow and cortical oxygen tension.⁵⁷

to complete resolution of oedema and to onset of symptom relief following a single dose of icatibant versus standard therapy.⁵³ However, icatibant had no appreciable benefit in treating ACE inhibitor-induced angioedema in a larger phase III trial (but in a non-comparable cohort of patients).⁵⁴ There is also limited evidence that a plasma-derived C-1 esterase inhibitor may improve rtPA-induced angioedema, but the overall evidence is limited.⁵⁵ ACE inhibitors may need to be stopped and substituted with an antihypertensive of another class in all cases of rtPA-induced orolingual angioedema. Bradykinin-mediated orolingual angioedema is not an absolute contraindication for the readministration of rtPA.

Orolingual angioedema that compromises airway and breathing, where airway obstruction is imminent or manifest, is an emergency and should currently be treated as such irrespective of its hypothesised mechanism. The local anaphylaxis protocol should be followed (box 2), and icatibant may be an adjunct treatment option.

CONCLUSION

While rare in the reported literature, our experience is that mild orolingual angioedema is not that infrequent

Key points

- ▶ Orolingual angioedema is an infrequent, usually mild but potentially life-threatening adverse effect of recombinant tissue plasminogen activator (rtPA).
- ▶ Orolingual angioedema is mediated either by bradykinin or histamine or both.
- ▶ Rapidly evolving rtPA-induced orolingual angioedema associated with urticaria and pruritus usually represents anaphylaxis.
- ▶ Gradually evolving rtPA-induced orolingual angioedema without urticaria or other systemic involvement is likely to be bradykinin mediated.
- ▶ Bradykinin-mediated orolingual angioedema may be refractory to antianaphylactic agents and often subsides spontaneously but may resolve with bradykinin B2 receptor antagonists.

after rtPA administration for stroke. It is often treated aggressively as though it is anaphylaxis. In fact, much of it is caused by elevated bradykinin through the action of rtPA, enhanced by concomitant use of ACE inhibitors and possibly worsened by insular ischaemia with autonomic manifestations. Most cases are mild and can be managed with careful observation of vital signs and with a full escalation plan to treat for anaphylaxis should further signs become apparent. Patients with orolingual angioedema who develop respiratory compromise should be managed in the intensive care unit. A selective bradykinin B2 receptor antagonist may ameliorate the severity of the condition.

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