**HOW TO UNDERSTAND IT: HYPERSENSITIVITY REACTIONS TO RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR**

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Abbreviations:

ACE angiotensin converting enzyme

ACE-I angiotensin converting enzyme inhibitor

AIS acute ischaemic stroke

ICH intracerebral haemorrhage

IgE immunoglobulin E

IV intravenous

OLAO orolingual angioedema

rtPA recombinant tissue plasminogen activator

tPA tissue plasminogen activator

Abstract

Recombinant tissue plasminogen activator (rtPA) is currently the only approved thrombolytic agent for the treatment of acute ischaemic stroke widely used in clinical practice. However, its use may result in haemorrhage and hypersensitivity reactions. Orolingual angioedema (OLAO) is an infrequent, often 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 bradykinin generation is the key driver of OLAO. Most patients with OLAO probably have a bradykinin induced syndrome. Monitoring is important because OLAO may evolve and compromise airways and a very small number have angioedema as part of a systemic anaphylaxis. There are no published guidelines for the treatment of rtPA-induced OLAO, although there is some evidence that those refractory to standard anti-anaphylactic agents may resolve with bradykinin B2-receptor antagonists. It is important that responses to OLAO are proportionate and that patients are closely monitored.

Keywords: orolingual angioedema, hypersensitivity reactions, recombinant tissue plasminogen activator, acute ischemic stroke, bradykinin, B2-receptor antagonists

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| Key points |
| * Orolingual angioedema (OLAO) is an infrequent, often mild but could potentially become a life-threatening adverse effect of recombinant tissue plasminogen activator (rtPA).
* OLAO is mediated either by bradykinin or histamine or both.
* rtPA-induced rapidly evolving OLAO that is associated with urticaria and pruritus usually represents anaphylaxis.
* rtPA-induced gradually evolving OLAO without urticaria and other systemic involvement is likely bradykinin-mediated.
* Bradykinin-mediated OLAO may be refractory to anti-anaphylactic agents and often subsides spontaneously but may resolve with bradykinin B2-receptor antagonists.
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Introduction

Intravenous (IV) thrombolysis is an effective therapy for acute ischaemic stroke (AIS)1, 2. Recombinant tissue plasminogen activator (tPA) is currently the only thrombolytic agent approved by National Institute for Health and Clinical Excellence to treat AIS3.

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 clot. Recombinant tPA (rtPA) is a ~~second-generation plasminogen activator,~~ homologous to natural human tissue-type plasminogen activator ~~and derived from either human melanoma cell line or Chinese hamster ovary cells. It is a serine protease endothelial enzyme~~ that binds to fibrin-rich clots, ~~via the fibronectin finger-like domain and the Kringle 2 domain. The protease action~~ cleaves the Arg/Val bond in plasminogen to form active plasmin. Plasmin~~, itself a serine protease,~~ breaks down the fibrin matrix of the clot, thereby promoting thrombolysis and reperfusion.

Increased plasmin activates the complement and kinin pathways leading to inflammatory cytokine upregulation, increased blood-mucosal and blood-brain barrier permeability and release of glutamate by glial cells4, 5.

rtPA can trigger hypersensitivity reactions mediated by histamine, bradykinin or possibly both. Hypersensitivity reactions following administration of rtPA include urticaria, pharyngeal or laryngeal oedema causing stridor, bronchospasm with wheeze and tachypnoea, hypotension and tachycardia6. They are typically secondary to mast cell degranulation and result in fluid shift away from the circulation (causing circulatory collapse) to tissues causing localised swelling which may compromise the respiratory tract. Angioedema is caused by a rapid increase in localised vascular permeability of submucosal or subcutaneous capillaries and post-capillary venules with localized plasma extravasation. Mast cell-derived histamine release causes angioedema often associated with urticaria.

Bradykinin mediated angioedema is typically isolated and manifest without itch, urticaria or systemic involvement. It is resulted from bradykinin induced increased in vascular permeability.

 rtPA may trigger either type of reaction or indeed both. In this article, underlying pathophysiological mechanisms and the clinical approach to the evaluation of rtPA-induced hypersensitivity reactions are reviewed.

What is anaphylaxis?

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 individuals7. The precise incidence of anaphylaxis to rtPA is unknown, but few published case reports8-10 indicates rare incidences. A study of 105 ischaemic stroke patients showed the anaphylaxis incidence up to 1.9% after rtPA9. Anaphylaxis has varied clinical presentations, but respiratory compromise with bronchospasm or laryngeal and pharyngeal oedema and cardiovascular collapse are most concerning as they may cause death or 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 anaphylaxis12. These are common comorbidities in ischaemic stroke patients. Anaphylaxis is likely to be more severe if rapid in onset and provoked by an IV agent13. Increased plasma tryptase and urinary histamine levels 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 recommended19. rtPA results in non-IgE-mediated anaphylaxis via complement activation that then causes mast cell degranulation and the release of histamine20.

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with:

Mucocutaneous

involvement

(pruritus,

ﬂushing,

urticaria,

angioedema)

and

one

of

the

following:

A.

Respiratory

complications

(wheezing,

stridor,

hypoxemia/cyanosis)

B.

Hypotension

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end-organ

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(enceph

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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, angioedema) *and* one of the following:* Respiratory compromise (wheezing, stridor, hypoxemia, cyanosis)
* Hypotension\* or end-organ damage (encephalopathy, kidney injury, etc.)
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| 2. | Two or more of the following occurring rapidly after exposure to an allergen:* Mucocutaneous involvement (pruritus, flushing, urticaria, angioedema)
* Respiratory compromise (wheezing, stridor, hypoxemia, cyanosis)
* Hypotension\* or evidence of end organ damage
* Persistent gastrointestinal symptoms (pain, nausea, vomiting)
 |
| 3. | Hypotension\* after exposure to a known allergen (minutes to several hours) |
| \*Hypotension in adults is regarded as systolic BP of <90 mm Hg or greater than a 30% decrease in systolic BP from the patient’s baseline. Adapted from11 |

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| Box 1 |
| UK Resuscitation Guidelines (2008) Emergency treatment of anaphylactic reactions Anaphylaxis is likely when all of the following 3 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, 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 can have only a decrease in blood pressure, i.e., a Circulation problem)
* (3) There can also be gastrointestinal symptoms (e.g. vomiting, abdominal pain, incontinence)
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What does anaphylactic angioedema look like?

Angioedema is characterized 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 OLAO 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 and urticaria are the most common manifestations of anaphylaxis (more than 90%)13. About half the patients with urticaria also have angioedema. Only 40% of patients have urticaria alone; 10% have isolated angioedema21. Patients with urticaria and angioedema tend to be more severe with the involvement of other systems compared with those with isolated angioedema21-23. Therefore, the approach to angioedema with urticaria should be the same as for urticaria, whereas isolated angioedema is different entailing a different clinical approach.

What does bradykinin-induced angioedema look like?

Angioedema without urticaria is a separate entity, termed primary angioedema26. Reported causes of primary angioedema are a deficiency of C1 esterase inhibitor, hereditary angioedema with normal C1 inhibitor level, angiotensin-converting enzyme (ACE) inhibitors (ACE-I) and rtPA. Although each of these forms of angioedema is thought to be bradykinin-mediated, the strength of the supporting evidence varies markedly.

ACE-I induced angioedema is uncommon and occurs in less than 1% of all ACE-I treated patients. It is, however, up to five times commoner in the African-Caribbean population27. Up to 20% may be life-threatening, especially when upper airway involvement occurs28. ACE-I induced angioedema differs from rtPA-induced angioedema as there may not be an obvious relationship between exposure to the drug and appearance of angioedema29. Although 50% of ACE-I induced angioedema may occur during the first week of therapy, in others it can develop years before later30, 31. In contrast, rtPA-induced angioedema evolves during rtPA infusion or in the first two hours afterwards32. rtPA-induced angioedema may occur in up to 45% of patients using ACE-I4.

Bradykinin and its related kinins are small peptides with pleiotropic biological effects, including vascular dilatation and increased vascular permeability both of which can lower blood pressure. Bradykinin breakdown is catalysed by ACE. Those on ACE-I experience an increase in the half-life of bradykinin enhancing its biological activity. rtPA cleaves off bradykinin from kininogen (a large plasma protein)4. 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 infarct in mice24, 25. Once bound to receptors, bradykinin exerts a potent pro-inflammatory and pro-oedematous effect by increasing blood-mucosal and blood-brain barrier permeability, inflammatory cytokine up-regulation, the release of glutamate by astrocytes and microglial activation4, 5

What is rtPA induced angioedema?

OLAO associated with rtPA treatment has been reported in up to 7.9% stroke patients9, 10, 32-35. This may be an underestimate because of the presence of aphasia or cognitive impairment which may confound identification of mild OLAO. It occurs during thrombolysis in half of the patients, and soon afterwards in the remainder36. The major proportion of rtPA-induced OLAO is thought to be bradykinin-mediated and is not associated with urticaria. OLAO 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 days37. Bronchospasm and hypotension are uncommon. While rtPA-induced OLAO is not associated with increased long-term disability, it may still be potentially life-threatening36.

The underlying mechanisms of rtPA-associated OLAO are that the plasmin generated not only breaks down fibrin and ‘dissolves’ the thrombus but also activates the complement and kinin pathways. If complement (C4a, C3a, and C5a) is activated, mast cell degranulation may be triggered with resulting histamine release (Figure 1)9. These mediators result in capillary leak, inflammatory cell recruitment and possibly cardiopulmonary anaphylaxis38. Therefore, while anti-alteplase IgE antibody associated anaphylaxis has been reported in acute stroke8, most rtPA induced type 1 hypersensitivity reactions are non-immunological. Less than 1.9% of AIS patients develop OLAO as a result of immediate hypersensitivity reactions to rtPA9. Histamine-induced OLAO manifestation is more rapid, typically lasts less than 24 hours and almost all patients develop urticaria alongside OLAO and rapidly progress to hypotension, laryngeal oedema and bronchospasm over minutes (Table 2).

rtPA via plasmin generation and kinin pathway up-regulation significantly increases the levels of bradykinin4, 5 (Figure 1). Bradykinin may lead to blood-mucosal and blood-brain barrier leakage leading to OLAO, cerebral oedema and intracerebral haemorrhage (ICH)39. In a mouse stroke model, pharmacological inhibition of the bradykinin pathway reduced the frequency of ICH, cerebral oedema and infarct volume induced by rtPA40. A large prospective study also reported a higher risk of symptomatic ICH in AIS patients who developed OLAO post rtPA36. However, this was not correlated with higher morbidity or mortality in those who developed OLAO compared to those who did not36.

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| Table 2: Clinical and therapeutic differences between histamine- and bradykinin-mediated orolingual angioedema |
| Clinical features | Histamine angioedema | Bradykinin angioedema |
| Onset | Rapid (minutes) | Slow (hours) |
| Duration | 12–24 hours | 48–72 hours or more |
| Urticaria/pruritis | Frequent | No |
| Laryngeal oedema | Possible | Possible |
| Bronchospasm | Frequent | Rare |
| Hypotension | Frequent | Rare |
| ICH and/or cerebral oedema | No | Possible |
| Therapy with H1 antihistamines, corticosteroids and epinephrine | Effective | Not effective |
| ICH, intracerebral haemorrhage; adapted from37 |

An increased risk of rtPA-induced OLAO has been associated with ACE-I intake, insular cortex ischemia and female gender in acute stroke patients32-34, 36, 41, 42. ACE-I intake in stroke patients leads to increased baseline bradykinin facilitating rtPA-induced bradykinin surge and OLAO mimicking C1 esterase inhibitor deficiency26. Drug withdrawal stops or drastically reduces angioedema risk in most patients, but 25% of may have recurrences43. Insular cortex ischaemia in some studies has been reported to increase the risk of rtPA-induced OLAO via sympathetic activation and subsequent peripheral vasoconstriction but this has been challenged in others9, 36, 41, 44. This may explain the higher frequency of rtPA-induced OLAO in acute stroke than myocardial infarction patients with a rate of 0.02%9. Female sex is an independent risk factor for rtPA-induced OLAO in stroke patients33, 41, 44. The female predominance of OLAO may be linked to sex hormones role in the regulation of inflammation and an increased immune response in women45, 46. Moreover, bradykinin-mediated hereditary angioedema attacks are more frequent just before or during menses47.

How do we manage it?

Most hypersensitivity reactions associated with rtPA resolve with cessation of 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 appropriate6. Most cases can be managed by careful observation. In patients 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 visualise the soft palate, and hoarseness or change of voice or stridor (evidence of laryngeal involvement) requires immediate airway assessment (Table 3). Intubation should not be delayed as swelling can progress quickly making intubation impossible and emergency tracheostomy a necessity49.

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| Table 3: Ishoo classification for monitoring severity of upper airway oedema. |
| 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 from48 |

Mild hypersensitivity reactions settle with H1 antihistamines and corticosteroid treatment. However, patients who develop rtPA-induced OLAO may be resistant to standard anti-anaphylactic treatment50, 51 probably due to an underlying bradykinin-driven mechanism.

Several therapies approved for the treatment of hereditary angioedema have been tested for rtPA-induced OLAO 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 activity52. A phase II randomized controlled trial including subjects with ACE-I induced angioedema showed substantially shorter time to complete resolution of oedema and to onset of symptom relief following a single Icatibant dose versus standard therapy53. On the other hand, Icatibant had no appreciable benefit in treating ACE-I 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 limited55. ACE-I may need to be discontinued and substituted with an antihypertensive of another class in all cases of rtPA-induced OLAO. Bradykinin-mediated OLAO may not need to be considered as an absolute contraindication for the re-administration of rtPA.

OLAO that compromises airway and breathing, where airway obstruction is imminent or manifest, is an emergency and should currently be treated as such irrespective of the hypothesized. The local anaphylaxis protocol should be followed (Box 2), and Icatibant may be an adjunct treatment option.

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| Box 2 |
| * Stop rtPA infusion, lie patient flat, elevate legs and manage airway.
* Give Adrenaline\* 0.5 mg (0.5 ml) of 1 in 1000 given IM into the anterolateral thigh with prolonged compression to minimise haematoma formation post rtPA. This may be repeated.
* Consider IV N-saline 500-1000ml fluid challenge.
* In adults, give Chlorphenamine 10mg slow IV (or IM) and Hydrocortisone 200 mg slow IV or IM. Adrenaline is safest and most effective given IM as the IV route may provoke lethal arrhythmias. Early administration of IM Adrenaline is key to avoiding deaths in anaphylaxis. The subcutaneous route is ineffective.
* Chlorphenamine and Hydrocortisone should be given slowly IV as further IM 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.
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| IM, intramuscular; IV, intravenous; N-saline, 0.9% saline; rtPA, recombinant tissue plasminogen activator; Adapted from56; Of note, adrenaline\* may decrease cerebral capillary blood flow and cortical oxygen tension57 |

Conclusion

While rare in the reported literature, our experience is that mild OLAO is not that infrequent after rtPA administration for stroke. It is often treated over 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-I and possibly worsened by insular ischaemia with autonomic manifestations. Much is 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 OLAO 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.

Further reading

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Authors contributions

VA and DOK wrote the manuscript, ACP reviewed, edited and approved the final version of the manuscript.

Competing financial interest

Authors declare no competing financial interest.

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Figure Legends

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, angiotensin converting enzyme inhibitor; C1INH, C1 esterase inhibitor; rtPA, recombinant tissue plasminogen activator.