A Novel Approach to the Treatment of Orolingual Angioedema After Tissue Plasminogen Activator Administration

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Orolingual angioedema is a rare adverse effect of tissue plasminogen activator (tPA), with an incidence of 1% to 5%. There are currently no published reports describing resolution of tPA-induced orolingual angioedema with complement inhibitor therapy. A 72-year-old man receiving home angiotensin-converting enzyme inhibitor therapy presented to the emergency department with newly developed orolingual angioedema after treatment with tPA for acute ischemic stroke. Therapy was initiated with intravenous methylprednisolone 125 mg, famotidine 20 mg, and diphenhydramine 50 mg, without significant improvement. Because of increased concern for airway protection, plasma-derived C1 esterase inhibitor was administered. Concerns about progressive and airway-threatening orolingual angioedema subsided 2 hours after administration, and invasive airway maneuvers were avoided. Orolingual angioedema is an infrequent, severe adverse effect of tPA for treatment of acute ischemic stroke. Complement inhibitors may be an additional therapeutic option for patients presenting with orolingual angioedema with potential airway compromise that is refractory to standard anaphylactic therapies. [Ann Emerg Med. 2016;68:345-348.]

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2016.02.019

INTRODUCTION

Orolingual angioedema can be a life-threatening crisis initiated by genetic factors or by certain foods, medications, infections, or stress. Hereditary angioedema has edematous and inflammatory consequences similar to those of other causes, but it is due to qualitative or quantitative dysfunction of C1 esterase inhibitor.[1,2] This can result in excessive release of bradykinin and histamine, leading to increased vascular permeability and edema. Icatibant, ecallantide, and plasma-derived C1 esterase inhibitor are approved hereditary angioedema treatments that target areas to prevent and reverse orolingual angioedema.

Orolingual angioedema is a rare adverse effect of tissue plasminogen activator (tPA) treatment of acute ischemic stroke, with a reported incidence of between 1% and 5%.[3-10] The frontal, insular, and peri-insular regions are often involved and are believed to play a role in the pathophysiology of stroke-associated angioedema. This association is thought to be due to proximity to the facial cortex, in conjunction with increased sympathetic tone and peripheral vasoconstriction, leading to cerebral dysregulation.[10,11] Orolingual angioedema developing after tPA administration for acute ischemic stroke may manifest as unilateral swelling of the lips, tongue, and face. The resultant edema is commonly contralateral to the ischemic lesion, which is believed to be due to the infarction's triggering autonomic dysfunction and vasomotor changes in the hemiparetic side.[10] Despite this distinct presentation, available literature has demonstrated equal representation of bilateral, contralateral, and ipsilateral edema.[5,7,11]

The proposed mechanism of tPA-induced orolingual angioedema is shown in Figure 1.[1,6,7,9,11] Plasminogen is activated to plasmin by tPA, which leads to fibrinolysis and activation of the complement cascade and kinin pathway. Complement cascade activation causes anaphylotoxin release, which results in bradykinin production and vasodilatation. Patients receiving angiotensin-converting enzyme inhibitors who also receive tPA may be at higher risk for angioedema.[3,4,7,10] Angiotensin-converting enzyme inhibitors block plasma kinases responsible for bradykinin inactivation, resulting in elevated baseline bradykinin concentrations. Complement activation, histamine release, and bradykinin release are believed to be the primary mediators of tPA-associated angioedema.[1,2,5-7,9-13] Given a lack of direct treatment for tPA-induced orolingual angioedema, the current treatment recommendations suggest supportive care, corticosteroids, epinephrine, and histamine antagonists.[3-5,7,9] There is potential to use hereditary angioedema therapies in patients presenting with tPA-induced orolingual angioedema refractory to the first-line therapies.

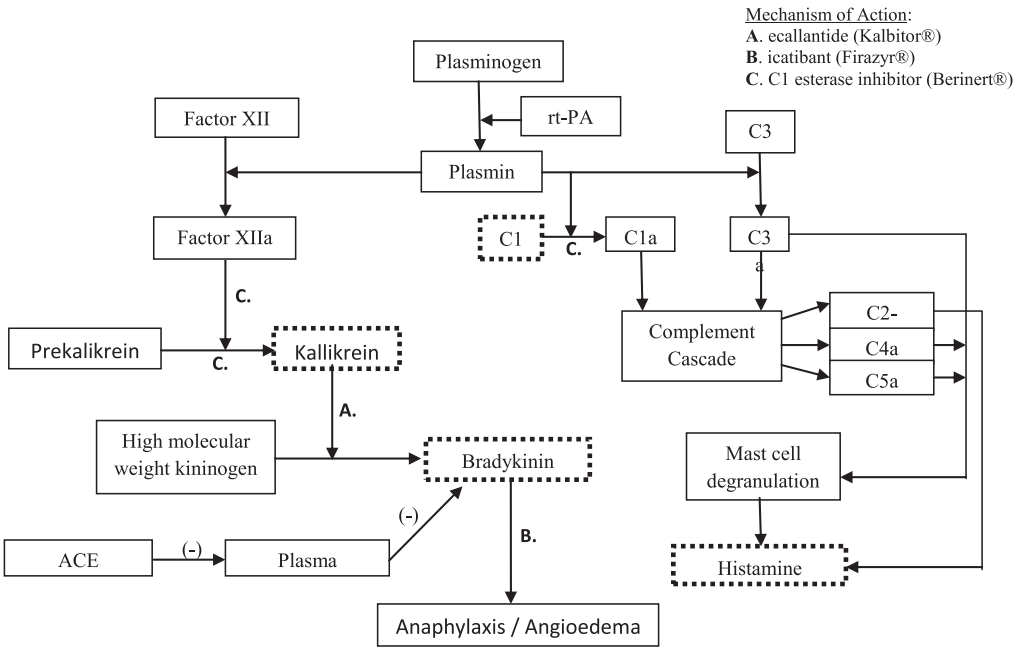

Figure 1. Mechanism of reaction. Potential treatment sites (dashed lines) are targeted throughout the cascade with histamine receptor blockers (famotidine and diphenhydramine), kallikrein inhibition (ecallantide [Kalbitor]), and bradykinin B2 competitive inhibition (icatibant [Firazyr]) and C1 esterase inhibition (C1 esterase inhibitor [Berinert]). The association with angiotensin-converting enzyme inhibitor occurs because of the inhibition of plasma kinases, which typically inactivate bradykinin. *ACE*, Angiotensin-converting enzyme. (Adapted with permission from Zarar et al,[9] Maertins et al,[13] and Lipski et al.[17])

CASE REPORT

A 72-year-old white man with a history of coronary artery disease, myocardial infarction requiring 2 drug-eluting stents, hypertension, and hyperlipidemia presented with sudden-onset right-sided weakness, dysarthria, and a National Institutes of Health Stroke Scale score of 10. Formal medication reconciliation was performed and included atenolol 25 mg, lisinopril 20 mg, hydrochlorothiazide 12.5 mg, atorvastatin 80 mg, aspirin 81 mg, and vitamin supplements. The patient received a diagnosis of acute ischemic stroke and also received intravenous tPA. Approximately 2 hours after tPA initiation, the patient developed tongue swelling and received diphenhydramine 25 mg intravenously during transfer to the comprehensive stroke center.

The patient was noted to have progressively worsening orolingual angioedema in transfer to the ICU but displayed improvement of right-sided weakness. He received methylprednisolone 125 mg, famotidine 20 mg, and diphenhydramine 50 mg intravenously within 5 minutes of presentation for symptomatic treatment of orolingual angioedema. Epinephrine was not administered at this time per prescriber discretion. Because of progressive tongue swelling, airway compromise, and the potential of a difficult airway in the context of recent thrombolysis, the interdisciplinary team decided to administer plasma-derived C1 esterase inhibitor for treatment of orolingual angioedema. Before and after administration of the plasma-derived C1 esterase inhibitor, values correlating with the complement cascade were evaluated by the on-site clinical laboratory. Plasma-derived C1 esterase inhibitor was administered within 2 hours of ICU arrival at 1,500 IU (20 IU/kg, rounded to the nearest vial size), with laboratory values evaluated pre- and posttherapy to assess biomarker response. C1 esterase inhibitor, C1 esterase inhibitor function, C4 binding protein, C4 complement, and tryptase were assessed to ensure that the C1 esterase inhibitor was not low in value or function, to evaluate whether levels further downstream in the cascade decreased after administration of the drug, and to observe the extent of mast cell degradation by using tryptase levels. All laboratory values were within normal ranges. No standardized plan was devised for these values to influence acute management or additional dosing because these were addressed by physical examination. Two hours after plasma-derived C1 esterase inhibitor administration, swelling associated with the orolingual angioedema began to visually improve per physical evaluation every 15 minutes. Potentially intubation or cricothyroidotomy were avoided (Figure 2).

The patient developed bilateral posterior parietal lobe intraparenchymal hemorrhages recognized by a clinical decline 6 hours after tPA was administered; this adverse