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Orolingual Angioedema After Tissue Plasminogen Activator Administration in Patients Taking Angiotensin-Converting Enzyme Inhibitors

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ABSTRACT
Orolingual angioedema is a rare adverse effect (1%–5%) of tissue plasminogen activator (tPA) that can lead to significant morbidity in patients with acute ischemic stroke. It is thought that increased levels of bradykinin and histamine resulting from tPA administration can result in angioedema. Angiotensin-converting enzyme (ACE) inhibitors can also lead to increased levels of bradykinin and appear to be a risk factor for tPA-associated angioedema. A literature review was conducted to examine previous cases of orolingual angioedema associated with tPA administration in patients also taking ACE inhibitors to better understand the relationship between ACE inhibitors and tPA-induced angioedema. Over a 20-year period, 27 patients who experienced angioedema with tPA while on ACE inhibitor therapy were identified. In this patient population, the onset of angioedema symptoms appeared as soon as 15 min after the tPA bolus and as late as 2 hr after the tPA infusion. Most patients required a combination of supportive medications such as corticosteroids (81.5%), antihistamines (74%), and epinephrine (18.5%) for the management of angioedema. Severe presentations of orolingual angioedema resulted in intubation for airway protection (26%). Symptom resolution ranged from shortly after the administration of supportive medications to 72 hr after symptom onset. Orolingual angioedema after tPA administration has the potential to cause significant morbidity, indicating patients should be monitored closely for a few hours after administration for the development of airway compromise. ACE inhibitors should not be the preferred antihypertensive agents for patients who require blood pressure lowering prior to tPA administration. **Key words:** ACE inhibitors, angioedema, tPA

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TISSUE PLASMINOGEN ACTIVATOR (tPA) is commonly used for the treatment of a variety of conditions such as ischemic stroke, pulmonary embolism, and ST-elevation myocardial infarction, and its use is supported by several national guidelines (Kearon et al., 2016; O'Gara et al., 2013;

Powers et al., 2018). Angioedema is a rapid swelling of the lips, face, and upper airway that is a rare but potentially life-threatening adverse effect of tPA administration. The incidence of angioedema after tPA for acute stroke has been reported to be 1%–5%, and may develop during or shortly after completion of the infusion (Correia, Matias, Calado, Lourenço, & Viana-Baptista, 2015; Myslimi et al., 2016). Vasoactive mediators such as histamine and bradykinin are often associated with the development of angioedema (Correia et al., 2015).

Tissue plasminogen activator (tPA) binds to thrombin and activates plasminogen to plasmin to induce thrombolysis (Bennett et al., 1987). Plasmin cleaves high-molecular-weight kininogen, which increases levels of bradykinin. It is thought that increased levels of bradykinin, a potent vasodilator, can contribute to the development of angioedema due to increases in vascular permeability and mucosal edema (Engelter et al., 2005). As outlined in Figure 1, plasmin can also contribute to the development of angioedema by increasing serum levels of anaphylatoxins like C3a, C4a, C5a, and C2 kinin, which leads to histamine release. Blood levels of C3a, C4a, and C5a have been shown to increase after tPA administration (Bennett et al., 1987). The presence of plasmin can directly activate C1, which leads to activation of the complement cascade. Due to this mechanism, hereditary or acquired C1 esterase inhibitor deficiency could be a risk factor for tPA-associated angioedema (Hill et al., 2000).

Angioedema is also a potential adverse effect of angiotensin-converting enzyme (ACE) inhibitors and is thought to occur in approximately 0.1% to 0.2% of patients (Baram, Kommuri, Sellers, & Cohn, 2013). Used for the treatment of hypertension and heart failure, ACE inhibitors may be taken frequently by patients who happen to present with acute ischemic stroke and other indications for which tPA may be administered. Similar to tPA, ACE inhibitors inhibit plasma kinases responsible for the destruction of bradykinin, leading to increased serum levels of bradykinin (Engelter et al., 2005).

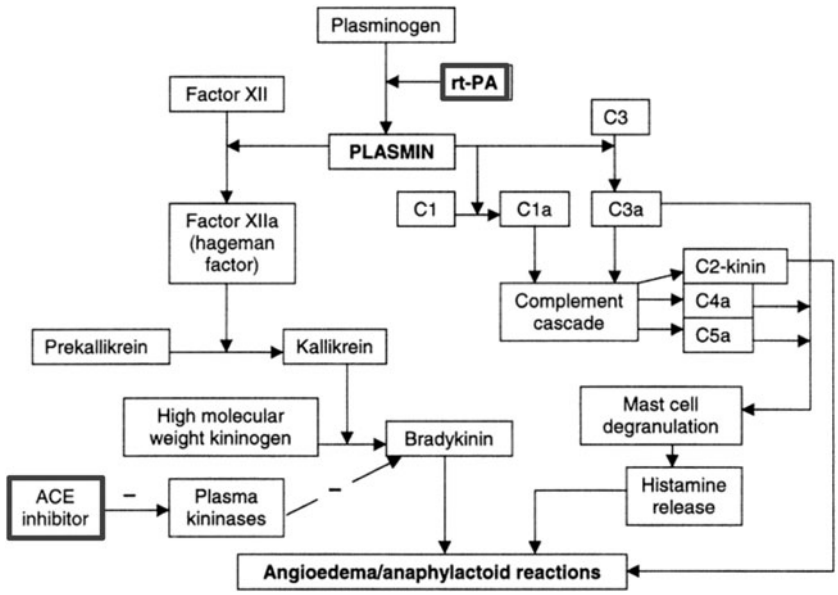

Figure 1. Mechanism of ACE inhibitor and tPA-associated angioedema. From "Anaphylactoid Reactions and Angioedema During Alteplase Treatment of Acute Ischemic Stroke," by M. D. Hill, P. A. Barber, J. Takahashi, A. M. Demchuk, T. E. Feasby, & A. M. Buchan, 2000, *Canadian Medical Association Journal*, *162*, pp. 1281–1284. Copyright 2000 by the Joule Inc. Reprinted with permission.

Bradykinin plasma levels in a patient taking an ACE inhibitor have been found to increase during an episode of angioedema, and then decrease once symptoms resolved (47 fmol/ml vs. 3.2 fmol/ml) (Nussberger et al., 1998). The similarity in pathogenesis of angioedema between tPA and ACE inhibitors begs the question of whether or not risk of development is increased when the two agents are combined.

The purpose of this review is to examine previous cases of orolingual angioedema associated with tPA administration in patients with acute ischemic stroke who are also taking ACE inhibitors to better understand the relationship between ACE inhibitors and tPA-induced angioedema. The exploration of this relationship is intended to provide health care professionals with a greater insight into the potential for orolingual angioedema occurrence, its presentation, and the subsequent management should it arise.

LITERATURE REVIEW

A literature review was conducted in PubMed using the MeSH terms "ACE inhibitors and angioedema," "tPA and angioedema," and "tPA, ACE inhibitors, and angioedema." Search results were analyzed by a single author (M.B.). Only articles published in English were reviewed. Further cases were identified by utilizing the references of relevant studies. Articles that involved the development of angioedema in the presence of ACE inhibitors without tPA administration were excluded. Articles with patients who received tPA for indications other than acute ischemic stroke were also excluded. In total 24 articles were included, including 15 case reports or case series, four retrospective single-center studies, one retrospective multicenter study, one prospective single-center study, one prospective multicenter study, and two review articles. Review articles were utilized for background information. Thirty-three additional articles failed to meet inclusion criteria (25 for angioedema without tPA administration, three for angioedema without ACE inhibitor use, two in a foreign language, two in vitro studies, and one animal study).

DISCUSSION

Although angioedema can occur after tPA administration in any patient, ACE inhibitor use appears to be an important risk factor. In one prospective evaluation of 172 patients with acute ischemic stroke treated with tPA, nine (5.1%) developed angioedema (Hill et al., 2003). The risk of developing angioedema with those taking an ACE inhibitor was compared with those taking beta blockers, calcium channel blockers, or angiotensin II receptor blockers (ARBs). Seven of the nine patients with angioedema were taking ACE inhibitors and five of the nine were taking beta blockers. The relative risk of developing angioedema if the patient was taking an ACE inhibitor was 13.6 (95% confidence interval [CI] = 3.0, 62.7), $p = .0002$. These results are consistent with a report of 33 people who experienced tPA-associated angioedema, 67% of which were taking an ACE inhibitor (Correia et al., 2015).

In a retrospective review of 559 patients who received tPA for acute ischemic stroke, five patients developed angioedema (0.89%) (Lin et al., 2014). Of all patients who received tPA, preadmission antihypertensive regimens included ACE inhibitors (3.8%), ARBs (17%), beta blockers (21.3%), and calcium channel blockers (21.3%). Two of the five patients with angioedema were taking ACE inhibitors. Table 1 shows the relative risk of ACE inhibitors on tPA-associated angioedema, where Lin et al. determined that the overall relative risk with ACE inhibitors was 12.9 (95% CI = 4.5, 37.0) (Engelter et al., 2005; Hill et al., 2003; Lin et al., 2014).

Table 2 summarizes the case reports, case series, and observational studies of patients with acute ischemic stroke who experienced angioedema with tPA while on ACE inhibitor therapy from 1997 to 2017 ($n = 27$). The average age of patients was 68.8 years and approximately 48% of patients were male. Onset of angioedema symptoms appeared as

Table 1. Relative risk for ACE inhibitors on tPA-associated angioedema compared with other antihypertensives

Authors	*n*	Angioedema (*n*)	ACE inhibitor (*n*)	ARB (*n*)	Beta blocker (*n*)	CCB (n)	Relative risk [95% CI]
Hill et al., 2003	176	9	7	0	5	0	13.6 [3.0, 62.7]
Engelter et al., 2005	120	2	1	N/A	N/A	N/A	5.3 [0.3, 81.4]
Lin et al., 2014	559	5	2	1	3	2	17.1 [3.0, 96.9]
Overall (Lin et al., 2014)	855	16	10	1	8	2	12.9 [4.5, 37.0]

Note. ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; CCB = calcium channel blocker; CI, confidence interval; N/A = not reported; tPA = tissue plasminogen activator.

soon as 15 min after the tPA bolus and as late as 2 hr after completion of the tPA infusion. Resolution of angioedema symptoms occurred as early as 2 hr after onset and as late as 72 hr after symptom onset. Management of orolingual angioedema ranged from no treatment to the administration of corticosteroids, antihistamines, epinephrine, or intubation.

The time to onset of tPA-associated angioedema for patients on ACE inhibitors was somewhat variable, because orolingual angioedema can occur during the tPA infusion as well as after completion of the infusion. There were two cases where angioedema occurred during the tPA infusion, and in one instance, the drip was stopped, an antihistamine, catecholamine, and cortisone were administered, and the patient was intubated (Yayan, 2012). In the second instance, the patient developed lingual angioedema and respiratory distress approximately 15 min after the tPA bolus (Correia et al., 2015). The patient received hydrocortisone, methylprednisolone, and epinephrine and the tPA infusion continued without further complications. The latest documented onset of angioedema symptoms was 2 hr after the tPA infusion (Correia et al., 2015). The timing of angioedema associated solely with ACE inhibitor therapy has been shown to occur after the first month of therapy in about 90% of cases, which differs significantly with the onset of tPA-associated angioedema in patients on ACE inhibitors (Banerji, Blumenthal, Lai, & Zhou, 2016). Although most severe cases of angioedema presented shortly after the tPA infusion, it is possible that severe symptoms could arise approximately 90 min after tPA is administered, as this is the length of time plasmin can activate the complement system (Krmpotic & Fernandes, 2007). In one case, the patient did not experience angioedema symptoms until 80 min after the tPA infusion and required diphenhydramine, hydrocortisone, epinephrine, and intubation (Lin et al., 2014).

In two cases, the patients' symptoms resolved spontaneously with no intervention (Lekoubou et al., 2014). However, four patients experienced prolonged symptom resolution where it took 48–72 hr for angioedema symptoms to resolve (Jahnke, 2003; Lin et al., 2014). Patients with prolonged symptom resolution were more likely to require intubation or cricothyroidotomy compared with those with symptom resolution in less than 48 hr (50% vs. 22%). This indicates that patients with a more severe presentation of angioedema should be expected to require supportive measures for a longer duration before their symptoms resolve. In patients with tPA-associated angioedema, symptom resolution almost always occurs within 24 hr (Lekoubou et al., 2014). Symptom resolution took longer than 24 hr in 15% of the

Table 2. Demographic and clinical characteristics of patients who experienced angioedema with tPA while ACE Inhibitor Therapy N = 27

	Gender	Age (year)	ACE inhibitor	PMH	Timing of symptoms	Resolution of symptoms	Management
Pancioli, Brott, Robertson, & Miller, 1997	Female	51	Enalapril	HTN, schizophrenia	Shortly after tPA infusion	Within 24 hr	Diphenhydramine 50 mg, methylprednisolone 125 mg
Hill et al., 2000	Female	76	Unnamed ACE inhibitor	Afib, CAD, HTN	30 min after tPA infusion	Several hours	Diphenhydramine 50 mg, methylprednisolone 80 mg, ranitidine 25 mg
Jahnke, 2003	Female	89	Enalapril	HLD, HTN, hypothyroidism	45 min into tPA infusion	48 hr	Diphenhydramine 50 mg, methylprednisolone 40 mg, cricothyroidotomy
Engelter et al., 2005	N/A	N/A	Unnamed ACE inhibitor	N/A	30 min after start of tPA infusion	Recovered—time frame not noted	Antihistamine, corticosteroid, intubated
Rafii, Koenig, & Ziai, 2005	Male	58	Benazepril	N/A	5 min after tPA infusion	48 hr	Antihistamine, dexamethasone
Krmpotic & Fernandes, 2007	Female	75	Lisinopril	DM, HLD, HTN	15 min after tPA infusion	Recovered—time frame not noted	Diphenhydramine, epinephrine, methylprednisolone, intubated
Khurana, Sharma, & Prabhakar, 2008	Female	50	Intravenous enalapril	N/A	Right after tPA infusion	24 hr	Antihistamine, corticosteroid
Maertins, Wold, & Swider, 2011	Male	66	Enalapril	HTN	Shortly after tPA infusion	Recovered—time frame not noted	Already intubated due to combativeness
Fugate, Kalimullah, & Wijdicks, 2012	Female	74	Lisinopril	HTN	Shortly after tPA infusion	Within 24 hr	Antihistamine, epinephrine, corticosteroid

(*continues*)

Table 2. Demographic and clinical characteristics of patients who experienced angioedema with tPA while ACE Inhibitor Therapy N = 27 (*Continued*)

	Gender	Age (year)	ACE inhibitor	PMH	Timing of symptoms	Resolution of symptoms	Management
Cheng, Lee, Jannes, Heddle, & Koblar, 2012	Female	73	Perindopril	Afib, HTN	Shortly after tPA infusion	24 hr	Adrenaline 1 mg IM, hydrocortisone 200 mg, prochlorperazine 25 mg, ranitidine 50 mg, intubated
Yayan, 2012	Male	63	Unnamed ACE inhibitor	DM, COPD, HTN	During tPA infusion	Recovered—time frame not noted	Antihistamine, catecholamine, cortisone, intubated
Foster-Goldman & McCarthy, 2013	Female	75	Lisinopril	DM, HLD, HTN, PE, prior stroke	20 min after tPA infusion	2 hr	Diphenhydramine, methylprednisolone
Gorski & Schmidt, 2013	Male	68	Lisinopril	Gout, HTN	30 min after tPA infusion	Several hours	Diphenhydramine, famotidine, methylprednisolone
Lekoubou et al., 2014	Male	69	Trandolapril	Afib, HTN	60 min after tPA infusion	3 hr	No treatment
Lekoubou et al., 2014	Male	68	Perindopril	Afib, HLD, HTN	35 minutes after tPA infusion	3 hr	No treatment
Lekoubou et al., 2014	Female	71	Lisinopril	DM, HLD, HTN	30 min after tPA infusion	24 hr	Antihistamine, corticosteroid
Lekoubou et al., 2014	Female	49	Ramipril	HLD, HTN	85 min after tPA infusion	24 hr	Antihistamine, corticosteroid
Lin et al., 2014	Male	78	Ramipril	HTN	80 min after tPA infusion	72 hr	Diphenhydramine, epinephrine hydrocortisone, intubated
Lin et al., 2014	Male	58	Enalapril	HTN	73 min after tPA infusion	4 hr	Hydrocortisone
Madden & Chebl, 2015	Male	50	Noncompliant with ACEi	Crack-cocaine abuse, HLD, HTN	Shortly after tPA infusion	48 hr	Dexamethasone 10 mg, diphenhydramine 50 mg, famotidine 20 mg

(*continues*)

Table 2. Demographic and clinical characteristics of patients who experienced angioedema with tPA while ACE Inhibitor Therapy N = 27 (*Continued*)

	Gender	Age (year)	ACE inhibitor	PMH	Timing of symptoms	Resolution of symptoms	Management
Correia et al., 2015	Male	76	Perindopril	DM, HTN	2 hr after tPA infusion	Recovered shortly after ice application	Ice application
Correia et al., 2015	Female	80	Captopril	HTN	15 min after tPA bolus (tPA infusion continued)	Recovered shortly after supportive medications	Epinephrine 0.5 mg, hydrocortisone 400 mg, methylprednisolone 180 mg
Correia et al., 2015	Female	79	Fosinopril	Afib, DM, HTN,	70 min after tPA infusion	Recovered shortly after supportive medications	Clemastine, hydrocortisone 200 mg, ranitidine
Correia et al., 2015	Male	62	Captopril	HTN	90 min after tPA infusion	Recovered shortly after supportive medications	Hydrocortisone 400 mg, hydroxyzine 25 mg
Correia et al., 2015	Female	89	Perindopril	DM, HLD, HTN	25 min after tPA infusion	Recovered shortly after supportive medications	Hydrocortisone 100 mg
Pahs et al., 2016	Male	72	Lisinopril	CAD, HLD, HTN	2 hr after tPA initiation	2 hr after C1 esterase inhibitor	Diphenhydramine 50 mg, famotidine 20 mg, methylprednisolone 125 mg, plasma derived C1 esterase inhibitor
Krishnaiah, McLaughlin, Lee, & Good, 2017	Male	70	Lisinopril	DM, HTN	30 min after tPA infusion	24 hr	Diphenhydramine, methylprednisolone, intubation

Note. ACE = angiotensin-converting enzyme; ACEi = angiotensin-converting enzyme inhibitor; Afib = atrial fibrillation; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HLD = hyperlipidemia; HTN = hypertension; N/A = not reported; PE = pulmonary embolism; PMH = past medical history; tPA = tissue plasminogen activator.

27 patients reviewed, indicating that ACE inhibitor use may prolong the symptoms of tPA-associated angioedema. Regardless of initial presentation and subsequent resolution of angioedema, most patients fully recovered from angioedema-related complications. However, in a retrospective study of patients who developed angioedema after tPA (7.9%), two patients died within 48 hr where severe airway compromise despite intubation was a large contributing factor (Hurford et al., 2014). It is unknown whether these patients were also taking ACE inhibitors.

Many patients required a combination of supportive medications to manage angioedema symptoms. Corticosteroids were administered in 81.5% of patients, with the most common agents being methylprednisolone and hydrocortisone. Most patients required at least one antihistamine (74%), and some patients received both an H1 receptor antagonist and an H2 receptor antagonist. Diphenhydramine was the most commonly utilized antihistamine and was administered in 37% of the patients reviewed. The use of epinephrine was often reserved for severe presentations of angioedema and was used in 18.5% of patients. In the most severe cases of angioedema, intubation was necessary for airway protection (26% of cases). This is slightly higher than the reported 20% of ischemic stroke patients who required intubation due to tPA-associated angioedema (Lekoubou et al., 2014).

Due to the small sample size and retrospective nature of the majority of the reviewed publications, there are several limitations associated with this review. Many case reports did not always document time to symptom onset and time to symptom resolution. Furthermore, the time frame between ACE inhibitor and tPA administration was often not discussed. In the patients whom the doses of supportive care medications were not documented, it is challenging to conclude whether patients were managed optimally. Most cases did not follow up patients for an extended period, so it is unknown whether the patients were restarted on ACE inhibitor therapy after symptom resolution. The inability to determine the precise percentage of the population on ACE inhibitor therapy makes it difficult to determine whether the proportion of patients with reported tPA-associated angioedema on ACE inhibitors reflects a significant increase in risk.

PRACTICAL APPLICATION AND MANAGEMENT

There is no direct reversal for tPA-induced orolingual angioedema; therefore, patients receive vigilant airway monitoring, symptom management, and supportive care. Health care staff should be aware of the most commonly utilized medications and interventions to control angioedema in this patient population to provide prompt treatment if symptoms arise. At the first signs of angioedema, it is usually necessary to turn off the tPA infusion, if it is still infusing. The 2018 Guidelines for the Management of Acute Ischemic Stroke recommend the administration of intravenous methylprednisolone 125 mg, diphenhydramine 50 mg, and ranitidine 50 mg, or famotidine 20 mg if patients experience tPA-associated angioedema (Level of Evidence C, expert opinion) (Powers et al., 2018). If patients do not respond to antihistamines and corticosteroids, epinephrine is often the subsequent supportive medication given for angioedema management. However, epinephrine was at times avoided in patients with acute ischemic stroke due to the potential risk of intracerebral hemorrhage with a sudden increase of blood pressure (Hill et al., 2000). Although other case reports demonstrate the ability to give epinephrine safely for tPA-associated angioedema, health care professionals should attempt to avoid the use of epinephrine in mild angioedema cases due to the theoretical risk for hemorrhage and limited number of cases. It is also possible that patients may not require any intervention if symptoms are minimal or if only lip edema is present—7% of patients in the review did not require any drug treatment.

The 2018 Guidelines for the Management of Acute Ischemic Stroke also include C1 esterase inhibitor and icatibant, a selective bradykinin B2 receptor antagonist, as other potential options for tPA-associated angioedema (Level of Evidence C, expert opinion) (Powers et al., 2018). It is notable that one patient in the review experienced symptom improvement (and avoidance of intubation) within 2 hr of receiving C1 esterase inhibitor, suggesting this agent may play a role in the future for patients with tPA-induced angioedema who are refractory to standard treatment (Pahs et al., 2016). However, these agents are costly, and the potential for C1 esterase inhibitor to cause thrombosis should be a consideration in those undergoing treatment for acute ischemic stroke (Crowther, Bauer, & Kaplan, 2014). Many hospitals may not routinely stock C1 esterase inhibitor or icatibant, as these agents are labeled for use in hereditary angioedema, but those in the emergency department should be aware of their potential utility and local availability if patients are not responding to standard supportive care measures.

The range in severity and onset of angioedema symptoms should demonstrate the need for frequent monitoring of the patient's tongue and oropharynx even a few hours after tPA administration when a patient has taken an ACE inhibitor. Angioedema with tPA administration has been reported to be about 5–17 times more common in patients on ACE inhibitors (Lin et al., 2014). Obtaining an accurate medication history may help clinicians to identify those patients who might be at high risk for angioedema from tPA administration. Since angioedema can progress rapidly, it would reasonable to monitor patients every 15 min during and after the tPA infusion for approximately 2 hr. The American Stroke Association recommends neurologic monitoring every 15 min for the first 2 hr in patients receiving tPA, indicating little additional time and resources would be needed to examine the tongue and oropharynx during scheduled neurologic assessments (Powers et al., 2018). Members of the health care team should be alerted as soon angioedema symptoms present to assess the need for intubation.

Orolingual angioedema also has the potential to occur after tPA administration in patients taking other antihypertensives, such ARBs. Three case reports of patients on ARBs who developed angioedema after tPA were examined and found that presentation of symptoms and management was similar to those who developed angioedema on ACE inhibitors after tPA administration (Hill et al., 2000; Lin et al., 2014; Tan, Tang, Lin, & Jeng, 2010). Two patients had mild symptoms that resolved in a few hours with diphenhydramine and hydrocortisone (Lin et al., 2014; Tan et al., 2010). In one of these cases, the ARB was restarted a week later (Tan et al., 2010). However, the third patient had a history of angioedema with ACE inhibitors and developed severe angioedema symptoms that required intubation (Hill et al., 2000). It appears that this is the only case that addressed a patient's previous history of angioedema with an ACE inhibitor who then developed angioedema after tPA administration while on an ARB. For these reasons, members of the health care team should be cognizant of the potential for orolingual angioedema to occur after tPA administration in the presence of antihypertensive medications that are not ACE inhibitors.

CONCLUSION

ACE inhibitors and tPA share a common mechanism for the development of angioedema, and patients who are currently on ACE inhibitors are at higher risk for angioedema if they receive tPA for acute ischemic stroke. Due to the potential for significant morbidity, patients should be monitored closely during tPA administration and for a few hours after administration for the development of airway compromise due to angioedema. Even though angioedema is more common in patients on ACE inhibitors, it is important to monitor all patients receiving tPA. Medical staff should examine the tongue and oropharynx periodically and

be prepared to administer supportive medications, such as corticosteroids, histamine receptor antagonists, and epinephrine, should angioedema arise. ACE inhibitors would not be preferred for patients who required blood pressure lowering prior to tPA administration, as they appear to have the highest incidence of angioedema compared with other antihypertensives. If the situation arises where a patient has a history of tPA-induced angioedema while taking an ACE inhibitor and presents with a new ischemic stroke, the risks versus benefits should be closely examined prior to subsequent tPA administration. Since there is not a large mortality associated with angioedema-related complications after tPA use, it would be reasonable to administer tPA if the potential benefit outweighs the risk of intubation. Regardless of history, patients should always be carefully monitored during and after a tPA infusion.

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