



Letter

Orolingual angioedema associated with olmesartan use after recombinant tissue plasminogen activator treatment of acute stroke

Recombinant tissue plasminogen activator (rt-PA) may cause angioedema, especially in patients who are using angiotensin-converting enzyme (ACE) inhibitors. Risk of angioedema has been reported to be associated with ACE inhibitor use (relative risk [RR], 13.6; 95% CI, 3.0–62.7).¹ Theoretically, angiotensin receptor blockers (ARBs) do not affect bradykinin and are regarded as good candidates to substitute for ACE inhibitors in patients with bradykinin-related adverse reactions to these drugs.² However, several studies have reported the occurrence of angioedema in patients using different ARBs. This article describes a patient who used ARBs and developed angioedema during rt-PA administration for acute stroke. Administration of steroids did not relieve the angioedema until olmesartan therapy was discontinued. To our knowledge, this is the first report about angioedema associated with the use of olmesartan during rt-PA administration.

The study was approved by the Institutional Review Board of Navy 411 Hospital. The patient provided written informed consent for the use and linkage of her medical and pharmacy records.

An 80-year-old woman presented with acute onset of left-sided weakness. She had a history of hypertension, for which no anti-hypertensive drug had ever been used, and had no history of angioneurotic edema, cerebrovascular disease, seizures, or diabetes. There was no family history of hereditary angioneurotic edema or known allergies.

On admission to the emergency department, blood pressure was 182/72 mm Hg, pulse was 70/min, and Glasgow Coma Scale score was 15. Neurologic examination revealed left-sided hemiparesis (left arm strength, 4/3; left leg strength, 3/3) and mild left facial paresis. Pinprick sensation on the left side of the patient was slightly diminished. Her initial National Institute of Health Stroke Scale score was 5. Axial diffusion-weighted cranial magnetic resonance scans displayed hyperintensity in the posterior limb of the internal capsule, and T1/T2 images showed normal signals. Hyperacute ischemic stroke was suspected, and thrombolytic therapy was initiated.

Urapidil was used for lowering blood pressure. Then rt-PA was administered (0.9 mg/kg), initially as an intravenous bolus of 7 mg and later as an intravenous infusion of 58 mg for 60 minutes. She was noted to have obvious improvement in the left facial palsy and marked resolution of her sensorimotor symptoms.

However, 6 minutes after the end of rt-PA infusion, she began experiencing difficult breathing, throat pain, dysarthria, and an odd sensation in her mouth (Fig 1). Physical examination revealed moderate swelling of the tongue and uvula and mild swelling of the lips. There was no obvious rash, nausea and vomiting, or abdominal

discomfort. Blood pressure, oxygen saturation, and consciousness were normal. There was no fever or infection index. The plasma IgE level, erythrocyte sedimentation rate, and complete blood cell differential count were within the reference ranges. The patient had normal C3, C4, and C1 inhibitor serum levels.

A diagnosis of angioedema was made on the basis of the findings mentioned above. Initially, rt-PA was suspected as the factor that contributed to the angioedema. After immediate administration of methylprednisolone (120 mg), dyspnea was improved in 20 minutes, whereas the tongue and uvula remained obviously swollen.

Afterward, olmesartan (20 mg/d) was used as an antihypertensive medication. However, obvious swelling of the tongue and uvula was noticed in the following 3 days when methylprednisolone (400 mg) was administered daily. In drug-induced angioedema, the close temporal relationship between drug administration and appearance of angioedema is usually the key element that makes obvious the identification and subsequent withdrawal of the offending medication.² Usually, angioedema would be relieved within 24 hours after withdrawal of the offending medication. However, in our patient, angioedema remained after discontinuation of rt-PA therapy for 3 days, indicating that other than rt-PA, olmesartan may also be associated with angioedema. Therefore, amlodipine (5 mg/d) was used instead of olmesartan, and angioedema was attenuated and resolved completely on day 10 of hospitalization.

Although the first case report on angioneurotic edema associated with thrombolysis in acute ischemic stroke was published in 1997,³ only a few case reports and a small case series have focused on this rare adverse effect of rt-PA administration in acute ischemic stroke. Angioedema have been reported to occur in 9 (5.1%; 95% CI, 2.3%–9.5%) of the 176 consecutive patients given alteplase for acute ischemic stroke.¹

Plasminogen activator is a serine protease that cleaves plasminogen to plasmin, which further cleaves thrombus-bound fibrin, resulting in the fibrinolytic effect that can also activate the complement cascade and kinin pathway. Bradykinin is metabolized by aminopeptidase P, ACE, and kinase I, whereas ACE and aminopeptidase P are its first and second main inactivating pathways, respectively. Kinase I represents a minor pathway unless ACE is inhibited.⁴ When ACE inhibitors couple with the rt-PA-induced kinin pathway, they may increase bradykinin significantly and induce anaphylactoid response or angioneurotic edema.

Some evidence suggests that for patients who develop angioedema when taking an ACE inhibitor, the risk of development of any subsequent angioedema when taking an ARB is between 2% and 17%. This information will aid clinicians in counseling patients regarding therapy options after development of angioedema due to ACE inhibitors.⁴

Drs Wang and Bi contributed equally to this work.

Disclosures: Authors have nothing to disclose.



Figure 1. This patient developed severe orolingual angioedema that involved the tongue, uvula, and lips within 6 minutes of completing recombinant tissue plasminogen activator infusion. The angioedema did not respond to steroids until olmesartan therapy was discontinued.

There are 2 types of angiotensin receptors: AT1 and AT2. Olmesartan is a highly potent antagonist of the AT1 receptor. The vasodilatory effect of ARBs is exerted by competitive blockade of the AT1 receptor. The functional role of AT2 receptor is not clear because of its low expression. AT1 and AT2 receptors generally oppose each other physiologically.^{5,6} Increased pressure in the thoracic aorta can activate angiotensin II–AT2 receptor binding, which stimulates endothelial nitric oxide synthase phosphorylation via a bradykinin B₂ receptor and protein kinase A–dependent pathway, which is not opposed by an ARB.^{5,7}

Another study reported that both losartan and eprosartan increased the serum bradykinin level in hypertensive patients because of reduced metabolism induced by ACE and neutral endopeptidase.⁸ Olmesartan may increase the serum bradykinin level and mediate angioneurotic edema via a similar pathway.

In our patient, angioedema seems to be the result of the synergistic effect of ARBs, rt-PA, and hypertension. To our knowledge,

this is the first report about angioedema associated with olmesartan during rt-PA administration. In addition, it is the third published case and the first case in an Asian patient of olmesartan-induced angioedema.^{9,10}

Shi Wang, MD, PhD*

Xiaoying Bi, PhD†

Lianbiao Shan, MD*

Yingqi Zhou, PhD*

*Department of Neurology

Navy 411 Hospital

Shanghai, People's Republic of China

†Department of Neurology

Changhai Hospital

Second Military Medical University

Shanghai, People's Republic of China

zhouyingqi81@163.com

References

- [1] Hill MD, Lye T, Moss H, et al. Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. *Neurology*. 2003;60:1525–1527.
- [2] Cicardi M, Zingale LC, Bergamaschini L, et al. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. *Arch Intern Med*. 2004;164:910–913.
- [3] Pancioli A, Brott T, Robertson V, et al. Asymmetric angioneurotic edema associated with thrombolysis for acute stroke. *Ann Emerg Med*. 1998;30:227–229.
- [4] Haymore BR, Yoon J, Mikita CP, et al. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. *Ann Allergy Asthma Immunol*. 2008;101:495–499.
- [5] Carey RM, Park J. Role of angiotensin type 2 receptors in vasodilation of resistance and capacitance vessels. *Hypertension*. 2006;48:824–825.
- [6] Carey RM. Cardiovascular and renal regulation by the angiotensin type 2 receptor: the AT2 receptor comes of age. *Hypertension*. 2005;45:840–844.
- [7] Hiyoshi H, Yayama K, Takano M, et al. Angiotensin type 2 receptor-mediated phosphorylation of eNOS in the aortas of mice with 2-kidney, 1-clip hypertension. *Hypertension*. 2005;45:967–973.
- [8] Campbell DJ, Krum H, Esler MD, et al. Losartan increases bradykinin levels in hypertensive humans. *Circulation*. 2005;111:315–320.
- [9] Vasquez JL, Jaramillo JC, Fernandez C, et al. Severe angioedema associated with olmesartan. *Ann Allergy Asthma Immunol*. 2011;107:285.
- [10] Nykamp D, Winter EE. Olmesartan medoxomil-induced angioedema. *Ann Pharmacother*. 2007;41:518–520.