



Incidence of orolingual angioedema after intravenous thrombolysis for stroke

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Abstract

Introduction Orolingual angioedema (OA) is a known adverse effect of intravenous (i.v.) alteplase. We analyzed all patients treated with i.v. alteplase for stroke at our hospital since approval of i.v. thrombolysis in Italy in 2004 to assess the incidence of this complication.

Patients and results Four hundred thirty-three patients received alteplase for stroke from April 2004 to May 2017. Two women developed OA (0.4%; 95% confidence interval 0.1 to 1.6%). Angioedema was mild in one case and severe in the other, with massive swelling of the lips, tongue, and oropharyngeal mucosa, and oropharyngeal bleeding, requiring intubation. Neither patient used ACE-inhibitors.

Discussion The incidence of orolingual angioedema was very low in our series. Although OA is usually mild, anaphylactoid reactions may rarely occur, because of the variable degree of activation of the complement system and kinin cascade caused by alteplase. In such instances, admission to neurointensive care may be required. Specific bradykinin antagonists or drugs that target the kallikrein-kinin system are beginning to be used in the more severe cases. Thus, doctors and nurses caring for acute stroke patients need to be able to recognize and treat this complication.

Keywords Stroke · Alteplase · Thrombolysis · Angioedema · Bradykinin

Introduction

Orolingual angioedema (OA) is a known adverse effect of intravenous (i.v.) alteplase that may present with different degrees of severity from mild lingual edema to massive swelling of the mouth and pharynx, requiring emergent medical therapy and intubation to allow adequate ventilation [1–3]. We analyzed the patients treated with i.v. alteplase for stroke at our hospital since approval of i.v.

thrombolysis in Italy in 2004 to assess the incidence of this complication.

Patients and methods

All patients treated with i.v. alteplase for stroke since 2004 were prospectively recorded in an electronic database which included age, sex, race, severity of stroke according to the NIHSS, alteplase dose, glucose levels before treatment, and ASPECTS score. Complications of alteplase, including symptomatic hemorrhage, death, fibrinogen level after thrombolysis, and orolingual angioedema were recorded as well. The presence of OA was checked with the same time schedule required for neurological surveillance after start of thrombolysis, that is, every 15 min for the first 3 h, than every 30 min for the following 5 h, than every hour up to 24 h after thrombolysis. Severity of OA, details of treatment, and outcome were extracted from the medical records at the time of hospitalization when OA occurred and were kept in a separate record.

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Results

Four hundred thirty-three patients received alteplase for stroke from April 2004 to May 2017. There were 251 men and 182 women. Mean $\pm$ SD age was 67.1 ± 13.1 years. The main demographic and clinical features are summarized in Table 1. No patient had been recently treated or was under active treatment with steroids, anti-histaminergic, or bradykinin receptor agonists at the time of thrombolysis. Two patients developed OA (0.4%; 95% confidence interval 0.1 to 1.6%). One was a 59-year-old woman of African origin, with a left-sided hemiparesis and a right hemisphere infarct involving the insula and the adjacent frontotemporal cortex. She developed mild edema of the lips and tongue, without side asymmetry, starting about 3 min after conclusion of the alteplase infusion. The edema disappeared within 24 h, without need for treatment. The second patient was an 83-year-old Caucasian woman with a left total anterior circulation infarct, who developed an anaphylactoid reaction, with massive swelling of the lips, tongue, and oropharyngeal mucosa, and oropharyngeal bleeding, a few minutes before the end of the alteplase infusion. Corticosteroids and adrenalin were immediately given, and the patient was intubated. She recovered from the edema in 36 h, but died because of brain herniation after 5 days. She had a previous severe allergic reaction to strawberries. None of the two patients was taking angiotensin-converting enzyme (ACE) inhibitors at the time of stroke, and fibrinogen levels before and after thrombolysis were normal in both patients.

Discussion

Orolingual angioedema has been described in 0.9 to 7.9% of patients receiving i.v. thrombolysis for stroke [1–4]. However,

its incidence was very low in our series. This difference may suggest that we have missed a few mild cases of OA, although this seems unlikely.

The mechanism of OA is thought to involve the production of bradykinin [5, 6], and the activation of the alternative complement pathway [7] by alteplase. Tissue plasminogen activator converts plasminogen to plasmin, which in turn cleaves bradykinin from high molecular weight kininogen [6]. This mechanism also explains the association between post-alteplase OA and ACE-inhibitor treatment consistently reported by several studies [1, 5, 8], because ACE-inhibitors reduce the clearance of bradykinin by kininases [5].

In both of our cases, the insular cortex was involved by the ischemic lesion. Insular damage has been related to OA after thrombolysis by some authors [5, 9], because of its putative role in autonomic regulation [10]. However, others have not found any correlation between acute insular lesions and development of OA after thrombolysis [1]. Orolingual angioedema is usually of mild intensity, but anaphylactoid reactions may occur, because of the variable degree of activation of the complement system and kinin cascade caused by alteplase [3, 6]. This complication may be severe enough to require intubation and admission to neurointensive care, as shown by our series and by others [8]. Lingual hematoma due to thrombolysis must sometimes be excluded as a cause of lingual swelling [8]. Since only two patients had OA and one of them (50%) had a history of allergic reactions, we feel that no statistically meaningful comparisons can be made regarding allergic reactions as a predictor of OA, although a history of such reactions should probably alert the clinician to a higher risk of OA after thrombolysis. Mild cases of OA need no treatment, or are usually given histamine antagonists (ranitidine and diphenhydramine), with or without corticosteroids [5]. In severe cases, steroids and epinephrine can be employed. However, OA due to alteplase depends more on bradykinin than histamine [6]. Clinically, itching and wheals are typical of histamine angioedema and are usually absent in bradykinin-mediated angioedema, although they may be absent also in idiopathic histaminergic-acquired angioedema [11]. Icatibant is a selective bradykinin B2 receptor antagonist given subcutaneously that is effective in acute attacks of hereditary angioedema due to C1 esterase inhibitor (C1-INH) deficiency or dysfunction [12] and has been licensed in Europe with this indication [13]. At least two reports have already described the prompt resolution of post-alteplase life-threatening OA after icatibant treatment in stroke patients, which avoided intubation [14, 15]. Thus, icatibant might be a therapeutic option for such rare very severe cases. Its cost (about 1700 euros) may be compensated by the avoidance of intubation and a shorter occupation of intensive care beds. Plasma-derived C1-INH, also used for angioedema associated with C1-INH deficiency, has been used in a severe case of post-thrombolysis OA too, with marked and quick benefit [16]. Another treatment employed in OA due to C1-INH deficiency,

Table 1 Demographic and clinical features

	<i>n</i> = 433
Age (mean $\pm$ SD)	67.1 $\pm$ 13.1 years
M: F	251:182
Hypertension	273 (63.0%)
Smoking	99 (22.9%)
Diabetes	57 (13.2%)
Atrial fibrillation	101 (23.3%)
NIHSS score (median)	14
ASPECTS (median)	10
Fibrinogen < 150 mg after thrombolysis	46 (10.6%)
ACE-inhibitors	69 (15.9%)
ARBs	155 (35.8%)

NIHSS National Institutes of Health Stroke Scale; ASPECTS Alberta Stroke Program Early CT Score; ACE angiotensin-converting enzyme; ARBs angiotensin II receptor blockers

the kallikrein inhibitor ecallantide has not been used in stroke patients, to our knowledge.

In conclusion, our series reinforces the notion that orolingual angioedema represents a specific item to monitor during alteplase infusion and the following hours. Doctors and nurses caring for acute stroke patients must be specifically instructed to seek it and be prepared to treat it, especially in patients taking ACE-inhibitors.

Compliance with ethical standards

The study was conducted in accordance with the Declaration of Helsinki and the medical ethics of our Hospital permitted analysis of the anonymous patient data.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was not obtained as only data required by the standard treatment protocol were used, and patient identity was kept anonymous.

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