CASE REPORT

Orolingual angioedema to alteplase. Identify, counsel and monitor at risk patients

Christopher Timmis,¹ Elliot Epstein,² Mohmad Salim¹¹Department of Anaesthetics, Walsall Manor Hospital, Walsall, UK²Department of Medicine, Walsall Manor Hospital, Walsall, UK**Correspondence to**
Dr Christopher Timmis,
c.timmis@nhs.net

Accepted 18 August 2016

SUMMARY

Orolingual angioedema (OLA) is a known complication of intravenous alteplase used to treat ischaemic stroke. The incidence may be as high as 5.1%. ACE inhibitors are thought to increase the risk of developing this potentially life-threatening complication. This case report demonstrates how we may improve in the identification of risk factors in the history; the counselling of patients appropriately; in seeking alternative therapies such as mechanical thrombectomy; and in the monitoring of patients for signs of OLA once alteplase has been given.

BACKGROUND

It may be possible to identify patients at increased risk of orolingual angioedema (OLA) if they are already taking ACE inhibitors.^{1–4} This may not change the decision to thrombolyse but could alter the consent process or intensify the monitoring of the patient after thrombolysis.^{1–4} General Medical Council (GMC) consent guidelines state that even if the likelihood is very small, a serious adverse complication should be discussed.⁵ OLA should therefore be discussed in the consent process, especially if the patient is on an ACE inhibitor. If alteplase is then administered, careful observation of the oral cavity should be carried out especially over the first 30–120 min.^{1–4} New medications are becoming available to treat certain types of angioedema and, having identified a patient at risk, it may prompt clinicians to locate the nearest available supply. It is worth noting that OLA can still occur in patients not taking ACE inhibitors and that ACE inhibitor-related angioedema is more common in Afro-Caribbean patients⁶ figure 1.

CASE PRESENTATION

A woman in her 70s presented with right hemiplegia and expressive dysphasia. She was a known hypertensive taking aspirin, simvastatin, ramipril and bisoprolol. She had no known allergies. Following prompt review by the stroke team, she was diagnosed with a total anterior circulation infarct and the patient was considered for thrombolysis. During the consent process, the risk of bleeding was discussed with the patient; this was followed by the administration of alteplase. Thirty minutes after completing the 1 hour course of treatment her relatives noticed lip and tongue swelling consistent with OLA. Her stroke symptoms remained unchanged. An urticarial rash was noted across her chest and forearm without respiratory or cardiovascular compromise.

INVESTIGATIONS

Unenhanced CT brain scan (figure 2) showed no evidence of haemorrhage. There was suggestion of presence of thrombus in the left middle cerebral artery; this is referred to as hyperdense middle cerebral artery sign (figure 2). Laboratory investigations: creatinine was elevated at 104 micromol/L; however, the patient did have a history of chronic kidney disease. Sodium, potassium, urea, full blood count and clotting profile were within normal limits. ECG showed atrial fibrillation. A post-thrombolysis CT scan (figure 3) confirmed features of a large infarction.

DIFFERENTIAL DIAGNOSIS

Apart from OLA, orolingual haematoma is an important differential which can be excluded on CT scan once the patient is stable.³

TREATMENT

Owing to concerns regarding her airway an urgent anaesthetic review was requested while hydrocortisone, chlorphenamine and intramuscular and nebulised epinephrine were administered. The decision was made to intubate the patient due to impending airway obstruction. She went to the intensive care unit and was extubated 12 hours later once the OLA had resolved. Collateral history revealed the patient had suffered previous episodes of tongue swelling and had a family history of tongue swelling. It was unclear if the episodes had occurred only since being on an ACE inhibitor.

OUTCOME AND FOLLOW-UP

The patient's stroke symptoms remained largely unchanged. C 1 esterase inhibitor levels were normal. Unfortunately the 4–6 hour mast cell

Figure 1 Patient with OLA. Adapted by permission from *BMJ Publishing Group Limited (Wallon et al,⁷ copyright notice year 2016)*. OLA, orolingual angioedema.

To cite: Timmis C, Epstein E, Salim M. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-216133

Figure 2 Unenhanced CT brain scan at the time of admission. There is a small hyperintense lesion (arrow) that may represent thrombus in the middle cerebral artery; this is referred to as hyperdense middle cerebral artery sign.

tryptase levels were not sent, initial tryptase and 24 hour tryptase levels were normal. The patient was discharged from hospital with unchanged stroke symptoms. The stroke consultant reviewed the patient in clinic. Unfortunately, she still had a dense right hemiparesis and expressive dysphasia; however, rehabilitation was on going. In view of non-valvular atrial fibrillation, rivaroxaban was started.

DISCUSSION

Wallon *et al*⁷ case report published in this journal reminds us of a potential incidence of up to 5.1% of OLA following alteplase and highlights the association with ACE inhibitors. This patient was on an ACE inhibitor and had a personal as well as family history of tongue swelling. Although there is significant time pressure when a patient is a candidate for thrombolysis, careful history taking could have shown an increased risk of OLA. This may not have changed the decision to thrombolysed but it may have prompted a discussion about OLA in the consent process and encouraged frequent review of the patient's oral cavity as Hill *et al* suggest. In this case it was fortunate the relatives noticed the OLA as monitoring of the patients oral cavity is not routine. Further research is needed to see if having a personal history or family history of tongue swelling increases the risk of OLA following alteplase.

Mechanical thrombectomy is performed in several tertiary referral centres in the UK. Meta-analysis has shown that mechanical thrombectomy, in addition to standard care, improves outcome for patients with acute stroke due to large vessel occlusion.⁸ However, if thrombolysis is contraindicated due to, for example, taking anticoagulants or a history of known hypersensitivity to alteplase then mechanical thrombectomy should be considered as first-line treatment.⁹⁻¹⁰ For centres that do not have onsite neuroradiological facilities, transfer to a tertiary referral centre may be necessary.

There is evidence suggesting hereditary and ACE inhibitor-induced angioedema can be treated with the selective bradykinin receptor-2 antagonist icatibant.¹¹⁻¹³ Icatibant is currently only licenced for hereditary angioedema.¹³ Alteplase activates both

Figure 3 Post-thrombolysis unenhanced CT brain scan. There is an area of low attenuation in the distribution of the left middle cerebral artery, consistent with a large infarction.

the complement and bradykinin pathways so there is potential for icatibant use in patients suffering with post-thrombolysis OLA.¹⁴ Bradykinin mediated reactions will not necessarily respond to standard treatments designed against histamine mediated allergy reactions.¹³ Case reports in this journal have suggested icatibant has reduced the need for emergency intubation of difficult airways following ACE inhibitor-induced angioedema.¹³

Patient's perspective

The patient was unable to give a perspective at the time or at follow-up due to her condition. Her relatives said, "good job we were here to notice she was swelling up".

Learning points

- ▶ We should consider informing patients and relatives regarding the risk of orolingual angioedema (OLA) prior to alteplase treatment and weigh up the benefits of alternative treatments such as mechanical thrombectomy if indicated and available.
- ▶ Higher risk patients include those taking ACE inhibitors; further research is needed to establish if personal or family history of tongue swelling increases the risk of OLA following thrombolysis.
- ▶ If decision is taken to thrombolysed patients at high risk it may change the post-thrombolysis period of observation and location of care.
- ▶ Careful monitoring of the oral cavity over the first 2 hours post-thrombolysis is recommended.
- ▶ Further research is needed to establish if new medications licenced for hereditary angioedema are effective in thrombolysis-induced OLA.

Contributors EE and MS have helped CT to produce this case report. They have contributed by suggesting ideas, helping to write and proof read the final article.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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