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Case Report

A patient with anaphylaxis after alteplase infusion

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ABSTRACT

Anaphylaxis to alteplase is a rare but reported complication of intravenous thrombolysis. We report a patient with a documented episode of anaphylaxis that occurred following an initial bolus and a subsequent delayed infusion of alteplase for thrombolysis of acute ischaemic stroke. The patient was treated with hydrocortisone, adrenaline, prochlorperazine and ranitidine, as per the hospital anaphylaxis protocol, intubation and admission to the intensive care unit. Serum tryptase levels performed during the anaphylactic event (at the end of the infusion) and 1.5 hours later showed an increase of 2 µg/L, suggestive of an anaphylactic reaction. Anaphylaxis remains largely a clinical diagnosis even in the absence of an elevated serum tryptase. The patient would benefit from further allergen testing given the severity of the reaction to alteplase. We report this patient to indicate that although rare, anaphylaxis is a recognised adverse event following alteplase. In the case of any symptoms suggestive of a minor anaphylactic reaction to alteplase, further infusion should be ceased to avoid a dose dependent major reaction.

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1. Introduction

The precise incidence of anaphylaxis to alteplase is unknown but with few case reports published in the past^{1,2} it would be expected to be an infrequent event. Adverse events data suggest that there have been four cases in over 1 million doses administered to date.¹ However, a study of 105 ischaemic stroke patients who were thrombolysed with alteplase post stroke indicated that the incidence of anaphylaxis may be as high as 1.9%,² suggesting the importance of this uncommon event. With the increasing use of alteplase for ischaemic stroke we report this patient with anaphylaxis as it is instructive.

2. Case report

A 73 year old Caucasian woman with known hypertension (treated with perindopril) and atrial fibrillation (on aspirin prophylaxis) presented to a tertiary hospital 70 minutes after the acute onset of left sided hemiparesis and hemisensory loss. She had no previous history of thrombolysis or airways disease. On arrival, the clinical features were in keeping with a right middle cerebral artery infarction corresponding to a National Institutes of Health Stroke Score (NIHSS) of 24. CT scan of the brain, revealed a

hyperdense right middle cerebral artery (MCA) in keeping with vascular occlusion. This was confirmed on CT angiography which also revealed thrombus extending into the ipsilateral intracranial internal carotid artery. Initial reporting concluded no features of infarction in the corresponding vascular territory. There were no other clinical, historical or laboratory contraindications for thrombolysis and following informed consent from the next of kin, a bolus dose of intravenous alteplase (5.9 mg bolus + infusion of 52.7 mg/hr) was commenced 100 minutes after symptom onset. Subsequent to this the CT report was revised by a senior colleague with features of major infarction affecting more than one half of the corresponding MCA territory. In view of this contraindication, alteplase infusion was aborted and the patient was transferred to another Stroke Unit within the metropolitan area for consideration of intra-arterial mechanical clot extraction.

On arrival to the second Stroke Unit, the patient was noted by nursing staff to be mildly tachypnoeic with an audible wheeze, which was unrecognised by the attending stroke physician at the time. The NIHSS was assessed to be 22. Repeat CT angiogram showed reperfusion of the right ICA and persistent occlusion of the right MCA second division. The corresponding CT scan of the brain scan also revealed improvement with changes of infarction restricted to the inferior division of the right MCA. This was not amenable to intra-arterial mechanical extraction and thus intravenous alteplase (59.4 mg over 60 minutes) was recommenced at 4 hours after symptom onset (3 hours following the initial bolus).

At the completion of the infusion of alteplase, which was 4 hours from the time of the initial bolus, the patient developed

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angioedema of the lips and tongue with increased respiratory distress. The anaphylaxis protocol at the hospital was immediately initiated, and comprised 200 mg intravenous hydrocortisone, 25 mg intravenous prochlorperazine, 50 mg intravenous ranitidine, and 1 mg intramuscular adrenaline. The patient was intubated and transferred to the intensive care unit. Normotension and normal oxygenation was maintained during this period of anaphylaxis. Serum tryptase levels were 2 and 4 µg/L (normal range <7 µg/L) at the end of alteplase infusion and 1.5 hours following onset of anaphylaxis, respectively. Eosinophil and basophil counts were not raised after the event.

A repeat CT brain at 24 hours post-alteplase infusion showed a small haemorrhage in the right internal capsule with mass effect and effacement of the right lateral ventricle. Extubation occurred the next day in the intensive care unit and the patient improved neurologically to a NIHSS of 18. However, the patient required a transfer to nursing home on eventual discharge.

3. Discussion

Anaphylactic reactions appear to be sporadic in tissue plasminogen activators, with clinical data suggesting that only alteplase and streptokinase have any reports of such reactions. As described previously, the incidence of anaphylaxis is as much as 1.9% in patients given alteplase for acute ischaemic stroke.²

The patient experienced angioedema at the conclusion of the alteplase infusion. There is a suggestion that concurrent use of an angiotensin converting enzyme (ACE) inhibitor and alteplase is associated with an increased risk of hemi-oro-lingual angioedema.³ The proposed mechanism is twofold. Plasmin activation of the complement cascade leads to the production of kinins contributing to angioedema, while direct activation of the kinin pathway leads to production of bradykinin and vasodilation. Meanwhile ACE inhibitors inhibit kininases responsible for the breakdown of bradykinin.² In a study of 176 patients, seven experienced angioedema with concurrent administration of an ACE inhibitor and alteplase³, however, none progressed to anaphylaxis. In this case we are unable to conclude if the prior use of an ACE inhibitor increased the risk of anaphylaxis.

Documentation of a raised serum tryptase level in the acute setting supports a diagnosis of anaphylaxis.⁵ However, a rise of 2 µg/L on serial serum tryptase levels taken during anaphylaxis to a sting challenge has been shown to have a 98% specificity and 73%

sensitivity for making this diagnosis. Serum tryptase levels are best compared with a baseline level. A concurrent histamine measurement resulting in either a raised tryptase or histamine level increases sensitivity of anaphylaxis diagnosis to 90%.⁴ Nevertheless, urinary histamine and serum complement levels are not currently recommended in the routine investigations of an anaphylactic reaction.⁵ One study has previously detected specific Ig E antibodies reactive to alteplase (anti-tPA IgE)¹, but this test is not currently available other than in research settings. Current guidelines suggest that following anaphylaxis, further allergen investigation and management by an immunologist or allergist is appropriate.⁵

In our patient, the possibility is raised that on initial alteplase bolus administration, the patient suffered a minor anaphylactic reaction that mounted into a full blown anaphylactic reaction after completion of alteplase infusion involving a much higher dose. Serum tryptase levels showed a rise of 2 µg/L but a more accurate picture of change of tryptase would have been obtained from a baseline serum tryptase level.⁶ Our patient would also have benefited from referral to an allergist given the severity of her reaction.⁵

In conclusion, Type 1 hypersensitivity reactions to alteplase may occur, albeit rarely. We would recommend caution in thrombolysis if a patient exhibits any signs or symptoms that are suggestive of anaphylaxis following the bolus infusion, as the severity of the reaction is dose dependent. Attention is necessary to observe any facial angioedema or respiratory distress during the administration of alteplase and to immediately institute management. A decision to proceed with alteplase administration in the first instance of a Type 1 hypersensitivity reaction should be made in the individual patient with a risk versus benefit analysis.

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