Successful intravenous thrombolysis following full dose rivaroxaban 5 hours before ictus

Introduction

Since the introduction of intravenous thrombolysis for acute ischaemic stroke a body of evidence has developed to help guide protocols for patients taking warfarin (Mazya et al, 2013). However, there remains a paucity of evidence as to the safety of intravenous thrombolysis in patients treated with novel oral anticoagulant drugs (Dempfle and Hennerici, 2011). This article reports a case of successful intravenous thrombolysis in an ischaemic stroke patient who was receiving prophylactic treatment with rivaroxaban for non-valvular atrial fibrillation.

Discussion

There is little evidence regarding the safety of intravenous thrombolysis in patients being treated with rivaroxaban. In the few previously reported cases, the interval between the last dose of rivaroxaban and onset ranged between 18 and 22 hours (Fluri et al, 2013; Seiffge et al, 2014). In this case, full dose (20 mg) rivaroxaban was taken much closer to ictus (5 hours) and to intravenous thrombolysis (8 hours).

Novel oral anticoagulant drugs are at least equally effective as warfarin for stroke prevention in patients with non-valvular atrial fibrillation and have more predictable pharmacokinetics (Connolly et al, 2009, Patel et al, 2011; Granger et al, 2011). With licenses for other indications, including treatment of venous thrombosis, the likelihood of encountering patients on novel oral anticoagulant drugs suffering acute ischaemic stroke is increasing. However, there is a lack of consensus among vascular neurologists regarding the assessment and treatment of such patients (Rybinnik et al, 2013).

More cases of intravenous thrombolysis have been reported in patients receiving the direct thrombin inhibitor dabigatran. The majority have not been complicated by intracerebral haemorrhage. A case complicated by fatal intracerebral haemorrhage had a relatively short interval of 370 minutes between stroke onset and last dose (Casado Naranjo et al, 2011).

Rivaroxaban has a half-life of 5–9 hours and it may cause prolongation of prothrombin time and activated partial thromboplastin time but these indexes are not reliable for measuring its pharmacodynamic effects. Anti-factor Xa activity assays may help indicate treatment effects but currently are not widely available within the time-critical window for intravenous thrombolysis. American Stroke Association and American Heart Association guidelines state that intra-venous thrombolysis is not recommended unless sensitive laboratory tests are normal or the patient has not

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Case Report

A 61-year-old man presented within 150 minutes of sudden onset right-sided hemiparesis and severe dysphasia. No medical records were available and an accompanying doctor was not aware of any significant medical history and confirmed that the patient did not take warfarin.

Examination revealed a left conjugate gaze palsy, a right upper motor neuron facial palsy and a homonymous hemianopia. Limb examination showed right-sided dense hemiparesis, hemisensory loss and sensory inattention. He had receptive and expressive dysphasia. His National Institutes of Health Stroke Scale (NIHSS) score was 21. His blood pressure was 144/86 mmHg, his blood glucose was 10.7 mmol/litre and 12-lead electrocardiogram revealed atrial fibrillation.

Cranial computed tomography showed early signs of left middle cerebral artery infarction with loss of grey-white matter differentiation in the left insula and temporal operculum extending into the left frontal cortex. Computed tomography arteriogram revealed occlusion of the distal M1 of the left middle cerebral artery with some collateral filling of the distal branches (*Figure 1*).

The patient developed an immediate (type 1) hypersensitivity reaction to contrast with facial swelling and rash. This was managed with intravenous hydrocortisone and chlorphenamine with rapid clinical improvement.

As no contraindication was known, intravenous thrombolysis was performed using standard dose tissue plasminogen activator (0.9 mg/kg) with an onset-to-needle time of approximately 180 minutes. Baseline blood tests were largely unremarkable with normal platelets and haemoglobin. His serum creatinine level was 99 umol/litre with an estimated glomerular filtration rate of 69 ml/min/1.73m^2. A coagulation screen sent before thrombolysis could not be processed and the decision to thrombolyse was taken without this information.

No complications were noted during the thrombolysis treatment or over the first hours of admission to the stroke ward post-thrombolysis. Routine cranial computed tomography approximately 24 hours post-thrombolysis showed no haemorrhage and a modest established acute infarct in the left middle cerebral artery territory (*Figure 1*). Stroke severity at 24 hours as measured by the NIHSS scale was 8. The patient improved clinically during the inpatient admission and his NIHSS score was 4 on discharge 8 days after admission.

When the full medical history became available, it was discovered that the patient was receiving treatment with rivaroxaban 20 mg daily for non-valvular atrial fibrillation, which he had most recently taken approximately 8 hours before receiving intravenous thrombolysis.

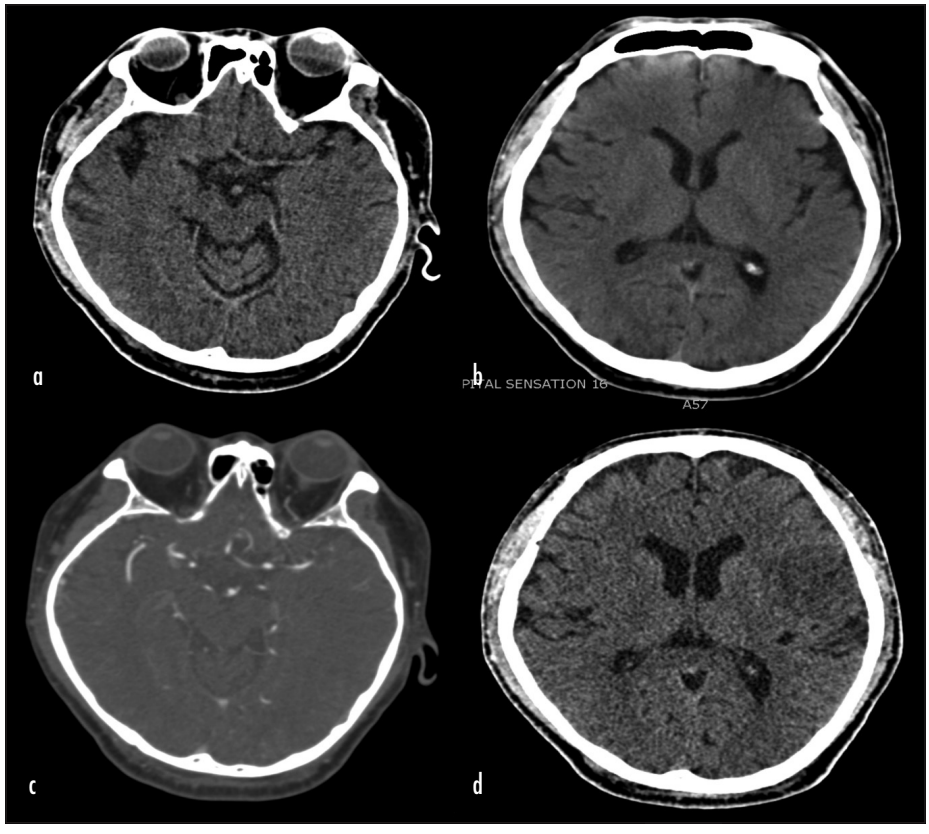

Figure 1. a. Cranial computed tomography showing a left hyperdense middle cerebral artery sign. b. Early ischaemic change in the left middle cerebral artery territory. c. Distal left M1 and proximal M2 segment occlusion on computed tomography arteriogram. d. 24-hour repeat computed tomography showing a left middle cerebral artery infarct without signs of haemorrhagic transformation.

LEARNING POINTS

- Whereas there is good evidence to guide intravenous thrombolysis decisions for patients taking warfarin, based on international normalized ratio, there is still a paucity of evidence regarding the safety of intravenous thrombolysis in patients receiving novel oral anticoagulant drugs.
- Guidelines suggest that intravenous thrombolysis should not be given unless sensitive laboratory tests are normal or the patient has not received a dose of a novel oral anticoagulant drug for over 2 days.
- The majority of reported cases to date of intravenous thrombolysis in patients receiving novel oral anticoagulant drugs have not been complicated by intracerebral haemorrhage.
- Wider availability of fast and reliable assays and more data from the use of intravenous thrombolysis in patients taking novel oral anticoagulant drugs are needed to help clarify decision making and construct guidelines.
- It is important for clinicians to be aware of issues relating to novel oral anticoagulant drugs given their increasing use for a growing number of indications.

received a dose of these agents for over 2 days (Jauch et al, 2013).

Wider availability of fast and reliable assays and more data from the use of intravenous thrombolysis in patients taking novel oral anticoagulant drugs are needed to help construct satisfactory guidelines and clarify decision making with regard to the risks and benefits of intravenous thrombolysis. **BJHM**

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