CASE REPORT

Intravenous thrombolysis in a patient taking warfarin with an international normalised ratio of 1.9

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SUMMARY

Intravenous thrombolysis is the mainstay medical treatment for acute ischaemic strokes, but has strict eligibility criteria. Symptomatic intracranial haemorrhage (sICH) is the most adverse complication. A woman aged 76 years presented with signs of an acute stroke and despite not meeting the eligibility criteria, given her background use of warfarin, she received intravenous thrombolysis with an excellent outcome. This is the first fully documented case report of the contraindicated use of intravenous thrombolysis in a patient presenting with an acute ischaemic stroke on a background of concurrent use of warfarin with an international normalised ratio (INR) as high as 1.9. It has been perceived that the risk of thrombolysis with a raised INR outweighs the potential benefits. However, documenting its use outside of the current eligibility criteria is key to future developments.

BACKGROUND

Currently, intravenous thrombolysis (rtPA) with alteplase is the only approved medical treatment for acute ischaemic strokes presenting within 4.5 hours of onset of stroke symptoms.^{1 2} A major complication of intravenous rtPA is the precipitation of a symptomatic, and potentially fatal, intracranial haemorrhage (sICH) which on average affects 1.7–8.8% depending on the sICH definition used.³ Therefore, based on risks versus benefits, there are strict protocols regarding eligibility for thrombolysis treatment. The European licensing for alteplase lists the use of oral anticoagulant such as warfarin as a contraindication.⁴ Acute stroke units within the United Kingdom often follow the American Heart Association(AHA)/American Stroke Association (ASA) guidelines which state that the use of intravenous rtPA is contraindicated if there is 'current use of anticoagulant with international normalization ratio (INR) >1.7 or partial thromboplastin (PT) >15 s'.⁵

CASE PRESENTATION

A Caucasian woman aged 76 years presented to the accident and emergency department accompanied by her son with a history of mixed receptive and expressive dysphasia since 09:00 that morning. At the time of admission, she was reviewed by the Stroke physician on call and noted to have right limb weakness and dysarthric speech. Her medical history included known atrial fibrillation, for which she was on warfarin, as well as a previous transient

ischaemic attack 4 years prior to her current admission. Admission bloods demonstrated an INR of 1.9 and an initial CT head showed no acute ischaemic changes or haemorrhage. Prior to admission, she lived alone and was independent in all her activities of daily living without any formal care support.

Two hours after admission and 3 hours after initial symptom onset, the patient developed a right homonymous hemianopia and worsening right hemiparesis. The patient and her son were understandably very distressed as there was now a high probability of significant disability, especially since her National Institute of Health Stroke Score (NIHSS) deteriorated from 5 to 11. Her son felt the patient would rather die than be left with a debilitating stroke. The risks of thrombolysis in the context of a raised INR were discussed with the patient's son, and on agreement, thrombolysis was performed. The total time from symptom onset to treatment was 3 hours and 47 min, and the door-to-needle time was 2 hours 47 min.

OUTCOME AND FOLLOW-UP

Twenty-four hours post-thrombolysis, the patient remained stable and her repeat CT head showed no haemorrhagic transformation. She had persisting mild dysarthria and dysphasia, which resolved by the time of discharge. She returned home and her modified Rankin score was 2 and her NIHSS improved to 2. The patient's follow-up MRI confirmed a small left hemispheric infarct. Her warfarin was discontinued as the stroke was deemed to be due to anticoagulation failure, and she was started on apixaban. She was discharged with the help of the Early Supported Discharge (ESD) team. She had no further episodes suggestive of focal neurological deficit at the time of her follow-up review, 2 months postdischarge. She had remained independent, with no care package and had resumed driving. She was therefore discharged from stroke clinic.

DISCUSSION

Based on eligibility criteria, only 15–20% of patients with an acute ischaemic stroke in England, Wales and Northern Ireland are expected to be eligible for thrombolysis treatment.⁶ In the Sentinel Stroke National Audit Programme (SSNAP), between July and September 2015, 11.6% of patients presenting with an acute stroke were reported as eligible, and 85.6% of these patients

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received thrombolysis.⁶ Therefore, an important reason for the current low thrombolysis treatment rates is the lack of eligible patients.

Thrombolysis in patients with a history of warfarin use and an INR of more than 1.7 is not recommended as it is deemed potentially harmful and associated with excess morbidity and mortality, with sICH being the most adverse complication.⁷ During the SSNAP audited period of July–September 2015, there was a reported 3.9% rate of sICH.⁶ The main challenge therefore in considering thrombolysis in patients who had acute stroke with a raised INR is the prospect of a severely disabling stroke versus a life-threatening intracerebral haemorrhage. As an absolute contraindication, clinicians are dissuaded from drawing from experience, or documented cases, in their decision-making.

There are at least 115 reported cases of patients receiving stroke thrombolysis with a background of concurrent use of warfarin and an INR of more than 1.7.⁷ Out of all these cases, there was only one documented sICH reported. Brunner *et al*'s⁸ single-centre series studied 36 patients with abnormal baseline coagulation, 29 of which had used oral anticoagulation leading to baseline INRs ranging from 1.4 to 1.9 and again found no significant difference in the rate of sICH or inpatient mortality. Xian *et al*⁹ documented an exploratory group of 33 patients with subtherapeutic INRs of more than 1.7 with only one reported incident of sICH. In this same study, a subgroup analysis of patients with an INR between 1.5 and 1.7 found no significant difference in the rates of sICH after adjustment for baseline clinical factors such as age and comorbidities.

Of note, the case presented not only challenges eligibility criteria but also time-to-treatment targets. The SSNAP found the average door-to-needle time for thrombolysis treatment was 53 min, but this significantly varies across acute stroke units in England, Wales and Northern Ireland.⁶ Although acute stroke prehospital and intrahospital pathways ensure rapid and accurate assessment and diagnosis, the thrombolysis time-to-treatment target is not often pragmatic. In the presented case, the door-to-needle time was 2 hours 47 min. During the patient's initial assessment, the perceived risk of haemorrhage from thrombolysis was higher than the likelihood of benefit. However, as her condition worsened, a re-evaluation of the risk versus benefit of thrombolysis prompted further consideration for intervention. Despite the pressure of a 4.5-hour target, it was essential, given the raised INR, that the risks of thrombolysis be discussed thoroughly with the patient and her family.

As well as time-to-treatment targets, broadening the thrombolysis eligibility criteria has also become a key area for improvement. For example, only recently was the treatment time window extended from 3 to 4.5 hours and the exclusion of patients on warfarin lifted for those with an INR <1.7.^{1 9} Further outcomes-based studies are needed to assess the safety and efficacy of thrombolysis in patients with INRs outside of the currently recommended eligibility range. At present, the lack of evidence means there is a limited understanding as to why certain cases of 'off label' thrombolysed patients have better functional outcomes and lower complication rates. Without explanation, it will be difficult to predict such successful outcomes in the future.

Although previously published cohorts of patients with an INR more than 1.7 did contain individuals whose INR was above 1.9, this is the first detailed case report of a patient with an INR at this level. If the INR threshold was to be broadened, the most important question would be to determine the level of

INR which would be an absolute contraindication to thrombolysis. More research is needed to assess the benefits and risks. Until then, it is unlikely that broadening the eligibility to include INR values of more than 1.7 would become part of clinical practice. However, this case demonstrates that at their discretion, senior clinicians may wish to explore this option on a case-by-case basis.

Learning points

- ▶ Intravenous thrombolysis for the treatment of acute ischaemic strokes has strict eligibility criteria.
- ▶ The concurrent use of warfarin and/or raised international normalised ratio (INR) is at present an absolute contraindication due to the risk of a symptomatic intracranial haemorrhage.
- ▶ This is the first detailed case report of the successful use of thrombolysis in a patient presenting with an acute ischaemic stroke and an INR of 1.9.
- ▶ More work is needed to determine ways to broaden the eligibility criteria for stroke thrombolysis treatment—one of these areas is the concurrent use of warfarin.

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