Is intravenous recombinant tissue plasminogen activator (r-tPA) safe in patients on Dabigatran?

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Abstract

Introduction—Dabigatran etexilate is a newly approved oral anticoagulant indicated for stroke prevention in nonvalvular atrial fibrillation. There are no reliable, rapidly available laboratory markers to assess its anticoagulant activity. There is no data on the safety of r-tPA on patients who are on dabigatran and it is not known whether r-tPA is safe in patients who are on dabigatran with a normal activated partial thromboplastin time (aPTT).

Case report—We report the case of a 59-year-old male who is reported with right hemiparesis and global aphasia. Two days prior to admission he underwent elective cardioversion for atrial fibrillation. He had begun dabigatran at 150 mg BID 3 days before cardioversion. Five days after commencing dabigatran, and 10 h after the last oral dose he presented with these symptoms. Patient fulfilled the criteria for r-tPA including a normal aPTT (30 s), normal prothrombin time (INR = 1.0) and a normal creatinine clearance (glomerular filtration rate >60 mL/min/1.73 m²). A brain CT without contrast was normal. After extensive discussion with the family, with clear understanding of the risks and benefits of such an approach in a patient who has been on dabigatran, consent was obtained, and r-tPA (0.9 mg/kg alteplase) was given. Patient’s hospital course remained uncomplicated and he was discharged 4 days after the initial symptoms to an acute rehabilitation facility and is currently on coumadin with INR therapeutic goal between 2 and 3.

Conclusion—More studies are needed to assess whether r-tPA might be safe in patients who are on dabigatran with a normal activated partial thromboplastin time and more than 10 h after the last dose.

Introduction

Dabigatran etexilate [Trade name: Pradaxa®] is a newly approved oral anticoagulant indicated for stroke prevention in nonvalvular atrial fibrillation. There are no reliable, rapidly available laboratory markers to assess its anticoagulant activity. Phase 2 trial of dabigatran concluded that activated partial thromboplastin time (aPTT) may provide a qualitative assessment of its anticoagulant activity but may not be suitable for accurately quantifying it. There is no data on the safety of r-tPA on patients who are on dabigatran and it is not known if r-tPA is safe in patients who are on dabigatran with a normal aPTT.

Case Report

A 59-year-old right-handed male reported with right hemiparesis and inability to speak for approximately 1 h. He has a history of rheumatic valvular cardiomyopathy (mitral regurgitation/ tricuspid regurgitation) with ejec-
Intracranial/extracranial brain MRA was unremarkable. Patient’s hospital course remained uncomplicated and he was discharged 4 days after the initial symptoms to an acute rehabilitation facility with a NIH score of 2. He completely recovered motor strength and facial movements and was left only with a mild expressive aphasia 3 months after the initial symptoms. Repeat noncontrast CT of the brain at 2 weeks, 2 months, 6 months follow-up showed a stable infarct size. Patient is currently on coumadin with INR therapeutic goal between 2 and 3.

**Discussion**

There are no randomized trials on the safety of r-tPA with dabigatran. Recent animal model study has shown that r-tPA might be safe in patients who are on dabigatran at routinely prescribed doses [1]. Two of the three previously published case reports on the safety of r-tPA did not have hemorraghic complications with thrombolysis [2,3]. Both had normal aPTT and were more than 5 h since the last dose. The one reported by Naranjo et al had a fatal intracerebral bleed with thrombolysis with a normal aPTT but within 5 h of the last dose (2.5 h since symptom onset) [4].

The Interventional Management Stroke (IMS) III trial proposed that administration of rt-PA or endovascular intervention could be considered 48 h after the last intake of dabigatran or within 48 h of last intake with normal aPTT [5,6].

But dabigatran has a nonlinear relationship with aPTT where by the concentration-response curve flattens at a concentration of >200 ng/ml [7]. The primary utility of aPTT is in its negative predictive value, as a normal aPTT suggests little anticoagulant activity [8,9].

In keeping with this, and without supportive literature on the safety of r-tPA in the context of dabigatran exposure, what treatment could neurologist do? We reasoned that his normal aPTT was of little clinical significance. Further it had been more than 10 h since his last dose and he would have been on the descending slope of the plasma levels since its half life is around 12–14 h [10]. Thus we concluded the benefits of r-tPA outweighed the risks in this urgent case scenario.

There is an increased risk of cerebral cardio embolism after cardioversion since the atrial “kick” is lost postprocedure. Whether dabigatran is efficacious in these high-risk cases remains unknown.

**Conclusion**

More studies are needed to assess whether r-tPA might be safe in patients who are on dabigatran with a normal activated partial thromboplastin time and more than 10 h after the last dose.

**References**