JVIN Journal of Vascular and Interventional Neurology
OFFICIAL JOURNAL OF THE ZEENAT QURESHI STROKE RESEARCH CENTER

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

Raghav Govindarajan and **Nestor Galvez**
CLEVELAND CLINIC FLORIDA

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 m^2). 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 asses 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 ejection fraction of 30%. 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 to hospital with global aphasia, right hemiparesis, and right upper motor neuron facial weakness. The initial NIH stroke score was 9. 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 m^2). 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. A Brain MRI done 16 h after the initial symptom onset showed an acute left middle cerebral artery infarct on the diffusion weighted imaging (Figure 1, arrow) with petechial hemorrhagic conversion (not shown).

Published May, 2014.

Raghav Govindarajan, Chief Neurology Resident, Department of Neurology, Cleveland Clinic Florida, CLEVELAND CLINIC FLORIDA, FL, USA, raghav316g@gmail.comNestor Galvez, CLEVELAND CLINIC FLORIDA, FL, USA, galvezn@ccf.org

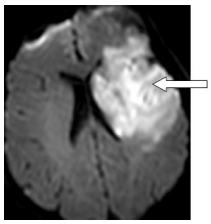

Figure 1. Axial diffusion-weighted MR image obtained 18 h from the initial symptoms shows a hyperintense lesion involving the left middle cerebral artery territory.

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 followup 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 hemmoraghic 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 dabigtran 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 dabigtran is efficacious in these high-risk cases remains unknown.

Conclusion

More studies are needed to asses 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

1. Pfeilschifter W, Bohmann F, Baumgarten P, et al. 2012;Thrombolysis with recombinant tissue plasminogen activator under dabigatran anticoagulation in experimental stroke. *Ann Neurol* 71(5):624–33.
2. De Smedt A, De Raedt S, Nieboer K, et al. 2010;Intravenous thrombolysis with recombinant tissue plasminogen activator in a stroke patient treated with dabigatran. *Cerebrovasc Dis* 30(5):533–4.
3. Matute MC, Guillán M, García-Caldentey J, et al. 2011;Thrombolysis treatment for acute ischaemic stroke in a patient on treatment with dabigatran. *Thromb Haemost* 106(1):178–9.
4. Casado, Naranjo I.; Portilla-Cuenca, JC.; Jiménez Caballero, PE., et al. 2011;Fatal intracerebral hemorrhage associated with administration of recombinant tissue plasminogen activator in a stroke patient on treatment with dabigatran. *Cerebrovasc Dis* 32(6):614–5.
5. CinicalTrials.gov. Interventional Management of Stroke (IMS) III Trial (IMS III). http://clinicaltrials.gov/ct2/show/NCT00359424December 27;2012
6. Watanabe M, Siddiqui FM, Qureshi AI. 2012;Incidence and management of ischemic stroke and intracerebral hemorrhage in patients on dabigatran etexilate treatment. *Neurocrit Care* 16(1):203–9.
7. van Ryn J, Stangier J, Haertter S, et al. 2010;Dabigatran etexilate-a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 103(6):1116–27.
8. Ezekowitz MD, Reilly PA, Nehmiz G, et al. 2007;Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol* 100(9):1419–26.
9. Watanabe M, Qureshi AI, Siddiqui FM. 2011;Periprocedural management of patients on dabigatran etexilate treatment. *Am J Neuroradiol* 32(8):E166.
10. Eisert WG, Hauel N, Stangier J, et al. 2010;Dabigatran: an oral novel potent reversible nonpeptide inhibitor of thrombin. *Arterioscler Thromb Vasc Biol* 30(10):1885–9.

Journal of Vascular and Interventional Neurology