CE
1.0 ANCC Contact Hour
1.0 Rx credit

Treatment With Intravenous Alteplase for Acute Ischemic Stroke After Reversal of Dabigatran With Idarucizumab: A Case Study

Sheila Jala, Elizabeth O'Brien

ABSTRACT

Treatment options for anticoagulated patients presenting with ischemic stroke are limited. Off-label use of idarucizumab to rapidly reverse the anticoagulant effect of dabigatran may ensure eligibility for thrombolytic therapy with alteplase. This case describes a 77-year-old white male who presented to the hospital 89 minutes after sudden onset of right-sided hemiparesis, dysarthria, and facial palsy. Significant history included atrial fibrillation and previous right-sided cortical stroke. Medication reconciliation revealed he was taking dabigatran 150 mg twice a day, with the last dose being 179 minutes before presentation. Neuroimaging revealed no new infarct or hemorrhage, and 60 minutes after arrival, a decision was made to give idarucizumab to reverse the anticoagulant effect of dabigatran. In the absence of any contraindication, he was then treated with intravenous alteplase and idarucizumab. No adverse outcomes were noted, and at discharge, his new stroke symptoms were completely resolved.

Keywords: alteplase, dabigatran, idarucizumab, ischemic stroke, thrombolytic therapy

CASE STUDY

Approximately 87% of all strokes are ischemic, and between 17% and 30% are caused by cardiac emboli.[1–3] Cardioembolic strokes are more disabling because they usually occlude large cerebral blood vessels affecting larger areas of the brain.[4] The most common source of cardiac emboli is left atrial thrombus due to atrial fibrillation (AF).[5] The risk of stroke in patients with AF increases 4- to 5-fold, related to age and the presence of vascular risk factors.[6] Moreover, the likelihood of stroke recurrence is relatively high in most cardioembolic sources.[6]

Idarucizumab, an agent to reverse the anticoagulant effects of dabigatran, was approved in 2015 for patients who develop serious bleeding or require urgent surgical intervention.[7] Idarucizumab is a humanized monoclonal antibody fragment that binds to dabigatran with very high affinity, approximately 300-fold higher than the binding affinity of dabigatran for thrombin.[7] As a consequence, idarucizumab binds free and thrombin-bound dabigatran, neutralizing its anticoagulant activity.[7] However, the safety and efficacy of its use for patients presenting with symptoms of acute ischemic stroke on dabigatran who are candidates for thrombolytic therapy are not yet fully evaluated. This case describes a patient with AF taking a therapeutic dose of dabigatran who developed an acute onset of ischemic stroke symptoms and was treated with idarucizumab before intravenous (IV) alteplase was able to be given.

Case Study

Mr J, a 77-year-old right-handed man, presented to a large tertiary hospital in New South Wales, Australia, in mid-2017 with right-sided hemiparesis, facial paralysis, and severe dysarthria. His medical history includes AF on digoxin and dabigatran 150 mg twice daily, ventricular tachycardia with an implantable cardioverter-defibrillator, hypertension (HTN) managed with enalapril and metoprolol, hypercholesterolemia on atorvastatin, and transient ischemic attack in 2013. Ten months before this presentation, he had a cardioembolic stroke affecting the right cerebral cortex, complicated by focal seizures managed with regular levetiracetam. Mr J had minimal residual

Questions or comments about this article may be directed to Sheila Jala, MHSS MCN, at Sheila.Jala@health.nsw.gov.au. She is the Stroke Clinical Nurse Consultant, Neurology Department, Royal North Shore Hospital, St Leonards, Australia.

Elizabeth O'Brien, GradDipNeuroSci, MNNP, is Stroke Nurse Practitioner, Neurology Department, Royal North Shore Hospital, St Leonards, Australia.

The authors declare no conflicts of interest.

DOI: 10.1097/JNN.0000000000000412

weakness to his left side 4+/5. He was independent with activities of daily living with a premorbid modified Rankin Scale (mRS) of 1. His risk of stroke measured by the stroke risk stratification in AF tool, $CHAD_2DS_2$-VASc, was 6 with 2 points for age of 75 years or older, 1 point for HTN history, 2 points for stroke history, and 1 point for vascular disease history; indicating he had a 13.6% risk of stroke/transient ischemic attack/systemic embolism.[8] His risk of major bleeding measured by the HAS-BLED scoring system for patients taking anticoagulants with AF was 4 with 1 point each for HTN, stroke history, age of older than 65 years, and medication use predisposing to bleeding; indicating he had a 1-year bleeding risk of 8.9%.[9]

On the day of his presentation, he took his 150 mg dose of dabigatran at approximately 8 AM. Approximately 90 minutes later, he complained of dizziness after leaning down to tie his shoelaces. His wife noticed a right facial droop, slurred speech, and right arm and leg weakness, which prompted her to call an ambulance. En route to the hospital, the paramedics observed worsening of his right arm and leg weakness and increasing drowsiness. He arrived at the emergency department at 10:59 AM with a National Institutes of Health Stroke Scale (NIHSS) score of 11. He was afebrile, blood pressure was 141/82 mm Hg, blood glucose level was 5.9 mmol/L, and oxygen saturation was 97% on room air.

While Mr J was in radiology for rapid noncontrast computed tomography (CT), a fluctuation of his symptoms was observed from baseline NIHSS score of 11 to 3 (2 facial paralysis and 1 for partial hemianopia) and then to 6 (3 for facial paralysis, 2 for complete hemianopia, and 1 for neglect). Noncontrast CT showed no acute infarct nor intracranial hemorrhage. It was initially decided when the NIHSS score dropped to 3 to stop the screening. However, when it increased again, all team members decided to proceed with screening for thrombolytic therapy. At this stage, the dabigatran level result showed it was within therapeutic range (Table 1). Coagulation studies showed an increased activated partial thromboplastin time, all other blood results were normal (Table 1), and there were no other exclusion criteria for thrombolytic therapy.

After discussions with the neurology, emergency, hematology, and clinical pharmacy teams, written consent was obtained from the patient's family to administer idarucizumab for dabigatran reversal, which was initiated at 12:03 PM. Two boluses of idarucizumab (2.5 g) were administered in succession. Fifteen minutes after the first bolus was given, repeat blood samples were taken and alteplase of 0.9-mg/kg bolus was administered immediately before the serum level returned. A low level of serum dabigatran (nanograms per milliliter) and a normal coagulation profile were returned; the infusion of alteplase was commenced. Mr J was admitted to the intensive care unit for postthrombolysis management. Within 1 hour, the symptoms had improved with limb weakness fully resolved, and NIHSS score was 2 (facial paralysis and quadrantanopia). After 2 hours, Mr J developed oral angioedema without airway compromise,

TABLE 1. Pathology Results: Electrolytes, Urea, and Creatinine and Coagulation Studies

	Value			
	11:00 AM	**12:30 PM**	**04:30 PM**	**Normal Range**
Electrolytes				
Sodium	135 mmol/L			135–145
Potassium	4.4 mmol/L			3.5–5.2
Urea	7.4 mmol/L			3.1–8.1
Creatinine	82 μmol/L			60–110
Coagulation				
aPTT	51.8 s[a]	31.7 s	32 s	24–36
INR	1.5[a]	1.1	1.2	
Fibrinogen level		3.8 g/L	2.89 g/L	2.00–4.00
TT		17.5 s	21.0 s	15.0–19.0
Factor assays				
Anti–factor Xa	162.1 ng/mL[a]	<35.0 ng/mL	<35.0 ng/L	
Dabigatran				
Platelet	161 × 10^9/L			150–400

Note. aPTT = activated partial thromboplastin time; INR = international normalized ratio; TT = thrombin time.
[a]Abnormal results.

which responded to treatment with IV hydrocortisone and ranitidine. There is a known increased risk of angioedema after alteplase with angiotensin-converting enzyme inhibitors;[10] therefore, this occurrence had been anticipated.

At 24 hours, the neurological examination showed a complete resolution of the right arm and leg weakness, vision, fluent speech, and very subtle facial paralysis (NIHSS score, 1). A repeat CT brain scan showed no evidence of hemorrhage or infarct. Antithrombotic therapy and deep vein thrombosis prophylaxis were initiated. Magnetic resonance imaging was not performed as Mr J's implantable cardioverter-defibrillator was not compatible with magnetic resonance imaging. CT angiography was conducted to provide clinical information on the degree and extent of arterial filling in the whole brain in a time-resolved manner.[11] This revealed a mild stenosis of the left internal carotid artery origin (<30%) and right internal carotid artery origin (<20%) due to calcified atheroma. Transthoracic echocardiography showed no evidence of intracardiac thrombus. Mr J's statin was increased to maximum dose for better management of low-density lipoprotein level (2.2 mmol/L). His blood pressure was elevated throughout the admission; therefore, amlodipine was added to his antihypertensive medications.

Throughout Mr J's hospitalization, the acute stroke nurse played a vital role in assessment, monitoring, and coordination of care. The nurse facilitated patient and family education regarding stroke care, dabigatran reversal, and secondary stroke prevention. The multidisciplinary team approach facilitated recovery. On day 4, Mr J had returned to his premorbid function (NIHSS score, 0; mRS, 1). The mRS is a tool used to measure the degree of disability or dependence in the daily activities of people who have had a stroke or other causes of neurological disability.[12] Other than the episode of oral angioedema, no further complications occurred during his hospital admission. Deep vein thrombosis prophylaxis was ceased, and he was continued on aspirin until day 5 poststroke when he was started on dabigatran 150 mg twice daily. He was discharged home with no need for ongoing rehabilitation.

Discussion

The current guidelines for thrombolysis treatment for patients with an acute ischemic stroke exclude those who are on therapeutic anticoagulation.[3] Mr J was successfully treated with alteplase after reversal of dabigatran with idarucizumab. His coagulation tests indicated a high dabigatran concentration (162.1 ng/mL) compared with 11 published cases, which had a median dabigatran concentration of 74 ng/mL.[13] Dabigatran is widely used in the prevention of embolic stroke in patients with nonvalvular AF and acts by inhibiting the enzyme thrombin, thereby preventing the development of blood clots.[11] It was found to be equivalent to warfarin with respect to the primary efficacy outcome of stroke, although intracranial hemorrhage rates were significantly lower.[14] In addition, dabigatran does not require regular monitoring and has fewer drug-drug interactions. Furthermore, it has more predictable pharmacokinetics with an absolute bioavailability of 6.5% after oral administration, meaning some patients receive double the effective dose, and 80% of the given dose is excreted by the kidneys.[14,15] Dabigatran's plasma concentration peaks 0.5 to 2 hours after oral administration, and its serum half-life is 12 to 17 hours, which makes it easy to manage dabigatran-associated bleeding by simply withholding the dose and providing supportive care for the patient.[14] In an acute ischemic stroke event with patients on dabigatran, current guidelines do not recommend thrombolytic treatment because of the high risk of bleeding.[16] Fatal intracerebral hemorrhage has been reported in 7 alteplase-treated patients on dabigatran, limiting treatment options for this cohort.[13] Patients with large vessel occlusion may be eligible for endovascular clot retrieval, whereas others may benefit from using idarucizumab.

Idarucizumab is a monoclonal antibody that directly binds to dabigatran and eliminates its anticoagulant effect.[17–19] Idarucizumab's binding to dabigatran is mediated by hydrophobic interactions, H-bonds, and a salt bridge, which result in a high affinity for dabigatran.[19] This high affinity corresponds with a rapid on-rate and a very slow off-rate, resulting in an almost irreversible binding of idarucizumab to dabigatran.[19] The reversal effects of IV idarucizumab were investigated in rats treated with dabigatran when both were given in an equimolar concentration.[19] Dabigatran alone prolonged thrombin time by 4-fold and activated partial thromboplastin time by 2-fold, over controls.[19] This anticoagulant activity was completely reversed by idarucizumab within 1 minute of administration.[19] Immediate and complete reversal of the anticoagulant effects of dabigatran by idarucizumab has also been demonstrated in healthy young volunteers with normal renal function, elderly volunteers aged 65 to 80 years, and volunteers aged 45 to 80 years with mild or moderate renal impairment.[19] After IV infusion in volunteers, idarucizumab concentrations peak within minutes and are followed by rapid elimination.[19] In the absence of dabigatran, idarucizumab has no effect on coagulation parameters or thrombin formation.[19] It was well tolerated at all administered doses in the phase 1 trials.[19]

Preclinical and early clinical data suggest that idarucizumab may provide safe and effective means of reversing anticoagulant activity in emergency situations

in patients treated with dabigatran.[17–19] Although its use has not been evaluated in clinical trials, there have been reported cases, including this case, with successful thrombolytic treatment after administration of idarucizumab.[13,20,21]

A recent review on the use of idarucizumab reversal of dabigatran concluded that giving alteplase after reversing dabigatran in acute ischemic stroke might be feasible for patients with less severe stroke in an early time window.[13] Our patient's profile meets these conditions (Table 2): he initially had an NIHSS score of 11, which dropped to 6; his symptoms were within the 4.5-hour period; and the next of kin was present providing relevant medical and social history and consented to the treatment plan. At that stage, despite the drop of the NIHSS score to 6, his symptoms remained debilitating.

The team consisting of paramedics, stroke nurse, neurologist, pharmacist, radiographer, interventional neuroradiologist, pathologist, and hematologist was responsible for the successful management of this patient. The team ensured timeliness of responding emergency calls, urgent transport to a thrombolyzing hospital, rapid assessment, imaging, and blood studies.

TABLE 2. Mr J's Hyperacute Treatment Timeline

Day/Time	Events
Day 0	
08:00	Oral intake of dabigatran 150 mg
09:30	Mr J experienced sudden onset of stroke symptoms
10:59	Arrival in emergency department; rapid assessment and history taking
11:05	Medication reconciliation and blood studies requested
11:08	Urgent brain imaging
11:30	Dabigatran level showed 162.1 ng/mL
11:55	Mr J and relatives consented dabigatran reversal and thrombolysis
12:03	First dose of idarucizumab given
12:10	Second dose of idarucizumab followed
12:18	Administration of alteplase and repeat blood test to check dabigatran level
12:30	Dabigatran level < 35.0 ng/mL and dilute thrombin time has normalized
12:45	Mr J developed angioedema
Day 1	Postalteplase monitoring as per protocol
Day 2	Mr J's stroke symptoms resolved
Day 3	Completion of stroke workup
Day 4	Mr J went home

The stroke nurse coordinated the entire process. She was responsible in the early detection of changes of Mr J's condition and adverse events and for contacting the multidisciplinary team especially the pharmacist, radiographer, and pathologist; providing information and support to the patient and family members; bed management; monitoring medication complications; and evaluating the patient's outcome. The experience of managing this patient reinforces the importance of developing a hospital-specific procedure or protocol for screening and administration of anticoagulation reversal to ensure timely, efficient, and safe use of reversal agents in this cohort of patients.

Conclusion

The use of idarucizumab rapidly normalizes the coagulation parameters of patients on dabigatran and was vital in this case of stroke. Idarucizumab was tolerated without unexpected adverse effects, hemorrhage, or procoagulatory complications. This case adds support for the safe use of idarucizumab in reversing dabigatran for patients who develop an acute ischemic stroke requiring thrombolytic therapy. Clinicians should consider dabigatran reversal for those who are otherwise eligible for thrombolysis. Further reporting of patients who receive this therapy will be of use in the absence of trial evidence. In addition, the role of the stroke nurse was vital in closely monitoring and evaluating the patient's condition and ensuring that team members were working together toward providing quality hyperacute stroke care.

References

1. Yiin GS, Howard DP, Paul NL, et al. Recent time trends in incidence, outcome and premorbid treatment of atrial fibrillation-related stroke and other embolic vascular events: a population-based study. *J Neurol Neurosurg Psychiatry*. 2017;88(1):12–18.
2. Widimsky P, Doehner W, Diener HC, et al. The role of cardiologists in stroke prevention and treatment: position paper of the European Society of Cardiology Council on Stroke. *Eur Heart J*. 2018;39(17):1567–1573.
3. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49(3):e46–e110.
4. Freeman WD, Aguilar MI. Prevention of cardioembolic stroke. *Neurotherapeutics*. 2011;8(3):488–502.
5. Carroll C, Barrett K. Cardioembolic stroke. *Continuum (Minneap Minn)*. 2017;23(1):111–132.
6. Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev*. 2010;6(3):150–161.
7. Huisman MV, Fanikos J. Idarucizumab and factor Xa reversal agents: role in hospital guidelines and protocols. *Am J Med*. 2016;34(11S):46–51.
8. Yaghi S, Kamel H. Stratifying stroke risk in atrial fibrillation: beyond clinical risk scores. *Stroke*. 2017;48(10):2665–2670.

9. Tsu LV, Berry A, Wald E, Ehrlich C. Modified HAS-BLED score and risk of major bleeding in patients receiving dabigatran and rivaroxaban: a retrospective, case-control study. *Consult Pharm*. 2015;30(7):395–402.
10. Wang YX, Li YQ, Zhang CH, et al. Analysis of related factors of orolingual angioedema after rt-PA intravenous thrombolytic therapy. *Eur Rev Med Pharmacol Sci*. 2018; 22(5):1478–1484.
11. Menon BK, d'Esterre CD, Qazi EM, et al. Multiphase CT angiography: a new tool for the imaging triage of patients with acute ischemic stroke. *Radiology*. 2015;275(2): 510–520.
12. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke*. 2007;38(3): 1091–1096.
13. Pikija S, Sztriha LK, Sebastian Mutzenbach J, Golaszewski SM, Sellner J. Idarucizumab in dabigatran-treated patients with acute ischemic stroke receiving alteplase: a systematic review of the available evidence. *CNS Drugs*. 2017;31(9): 747–757.
14. Kim YH, Roh SY. The mechanism of and preventive therapy for stroke in patients with atrial fibrillation. *J Stroke*. 2016;18(2):129–137.
15. Faria R, Spackman E, Burch J, et al. Dabigatran for the prevention of stroke and systemic embolism in atrial fibrillation: a NICE single technology appraisal. *Pharmacoeconomics*. 2013;31(7):551–562.
16. Fugate JE, Rabinstein AA. Absolute and relative contraindications to IV rt-PA for acute ischemic stroke. *Neurohospitalist*. 2015;5(3):110–121.
17. Glund S, Stangier J, Schmohl M, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. *Lancet*. 2015;386(9994):680–690.
18. Pollack CJ, Reilly P, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511–520.
19. Reilly PA, van Ryn J, Grottke O, Glund S, Stangier J. Idarucizumab, a specific reversal agent for dabigatran: mode of action, pharmacokinetics and pharmacodynamics, and safety and efficacy in phase 1 subjects. *Am J Med*. 2016; 34(11S):26–32.
20. Vosko MR, Bocksrucker C, Drwila R, et al. Real-life experience with the specific reversal agent idarucizumab for the management of emergency situations in dabigatran-treated patients: a series of 11 cases. *J Thromb Thrombolysis*. 2017;43(3):306–317.
21. Agosti S, Casalino L, Rocci E, Zaccone G, Rota E. Successful intravenous thrombolysis for ischemic stroke after reversal of dabigatran anticoagulation with idarucizumab: a case report. *J Med Case Reports*. 2017;11(1):224.

For more than 111 additional continuing education articles related to neurological topics, go to NursingCenter.com/CE.

Instructions:
- Read the article. The test for this CE activity can only be taken online at www.NursingCenter.com/CE/JNN. Tests can no longer be mailed or faxed. You will need to create (its free!) and login to your personal CE Planner account before taking online tests. Your planner will keep track of all your Lippincott Professional Development online CE activities for you.
- There is only one correct answer for each question. A passing score for this test is 13 correct answers. If you pass, you can print your certificate of earned contact hours and access the answer key. If you fail, you have the option of taking the test again at no additional cost.
- For questions, contact Lippincott Professional Development: 1-800-787-8985.

Registration Deadline: December 4, 2020

Disclosure Statement:
The authors and planners have disclosed that they have no financial relationships related to this article.

Provider Accreditation:
Lippincott Professional Development will award 1.0 contact hour for this continuing nursing education activity. This activity has been assigned 1.0 pharmacology credits.

Lippincott Professional Development is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is also provider approved by the California Board of Registered Nursing, Provider Number CEP 11749 for 1.0 contact hour. Lippincott Professional Development is also an approved provider of continuing nursing education by the District of Columbia Board of Nursing, Georgia Board of Nursing, and Florida Board of Nursing, CE Broker #50-1223.

Payment:
- The registration fee for this test is $12.95.
- AANN members can take the test for free by logging into the secure "Members Only" area of http://www.aann.org to get the discount code. Use the code when payment is requested when taking the CE test at www.NursingCenter.com/CE/JNN.