Title: Adverse Clinical Outcomes After Dabigatran Reversal With Idarucizumab To Facilitate Acute Stroke Thrombolysis

Authors:

Felix C Ng, (MBBS/BMedSc, MPH, DCH). Department of Neurology, Northern Health, Victoria 3076, Australia. Ng.fcffelix@gmail.com

James Bice, (MBBS) Department of Neurology, Northern Health, Victoria 3076, Australia.

James.Bice@nh.org.au

Anne Rodda (BN, MN(NP)) Department of Neurology, Northern Health, Victoria 3076, Australia.

Anne.Rodda@nh.org.au

Matthew Lee-Archer, (MBBS, FRACP), Department of Neurology, Northern Health, Victoria 3076, Australia. Matt.LeeArcher@nh.org.au

Douglas E. Crompton, (MBBS, PhD, FRACP), Department of Neurology, Northern Health, Victoria 3076, Australia. douglas.crompton@unimelb.edu.au

Corresponding author:

Felix C Ng, Department of Neurology, Northern Health, Victoria 3076, Australia. Phone: + 614 84508000, Email: ng.fcffelix@gmail.com

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Figure 1: *Adverse clinical outcome in two patients with idarucizumab-facilitated thrombolysis*

Table 1: *Summary of six reported cases to date*

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None reported

Adverse clinical outcomes after dabigatran reversal with Idarucizumab to facilitate acute stroke thrombolysis

Dear Sirs,

Intravenous tissue plasminogen activator (tPA) thrombolysis remains the only proven pharmacological treatment for acute ischemic stroke¹. A common clinical scenario is where a patient with atrial fibrillation (AF) on therapeutic anticoagulation presents with an acute ischemic stroke but thrombolysis is absolutely contraindicated due to hemorrhagic risk.

Recently, dabigatran reversal with idarucizumab to facilitate thrombolysis in acute stroke patients on dabigatran has been proposed². We present two patients, the first outside Europe, managed with this approach (Figure 1).

Case 1: A well 85-year-old presented with a severe dominant hemispheric stroke with a National Institutes of Health Stroke Scale (NIHSS) of 30 within 17 hours of last dabigatran dose. Computed Tomography (CT) with Angiogram and Perfusion studies showed a tandem left Internal Carotid Artery and Middle Cerebral Artery (ICA-MCA) occlusion with minimal established infarction and a large salvageable penumbra. Coagulation studies revealed isolated elevated Thrombin Time (>60 seconds, normal range <21 seconds) consistent with active dabigatran anticoagulation. 5g idarucizumab followed by tPA were administered at 167 minutes from symptoms onset. Mechanical thrombectomy was not possible as the patient arrived at an endovascular-capable centre outside the 6 hour therapeutic time window **after urgent inter-hospital transfer post-thrombolysis**. Day-1 CT showed a large hemispheric infarct with significant hemorrhage and mass effect. He progressively deteriorated and died on day 4.

Case 2: A 46-year-old with AF presented with left hemiparesis (**admission** NIHSS 5) within 1 hour of dabigatran intake. Multimodal CT revealed a right frontal ischemic penumbra without large vessel occlusion or stenosis. Idarucizumab and immediate tPA were administered at 178 minutes from onset with near-total resolution of symptoms (NIHSS 1). Follow-up CT confirmed a small area of right frontal infarction. At 30 hours, he developed a severe contralateral left hemispheric stroke (NIHSS 18) secondary to a **left** M2 segment MCA thrombus which was too distal for endovascular clot retrieval. With the recent stroke contraindicating further thrombolysis, he was conservatively treated. Subsequent echocardiogram did not reveal intracardiac thromboses or valvular lesions. He remained aphasic and bed-bound at 3 months.

Idarucizumab, a humanised monoclonal antibody fragment, was approved by the European Medicine Agency in 2015 as a reversal agent in patients on dabigatran requiring emergency procedures, or with life-threatening bleeding³. In-vitro and in-vivo studies with healthy controls have shown immediate normalization of dabigatran-induced anticoagulation following idarucizumab without prothrombic effects⁴⁻⁵. Based on these results, idarucizumab-facilitated thrombolysis in dabigatran-treated stroke patients has been endorsed by international expert opinion. However real-world clinical data are sparse with only six cases described^{3,6-10}, with the majority reporting favorable clinical outcomes without complications (Table 1).

The patients reported here have inherent risk factors for their adverse events irrespective of idarucizumab use. The high NIHSS and presence of major arterial occlusion in case 1 predispose to hemorrhagic transformation¹¹, while the increased risk of early stroke recurrence is well recognized in patients with cortical infarcts and AF as in case 2¹². Although we acknowledge there is insufficient information to conclude whether idarucizumab directly contributed to the adverse

outcomes, the development of both major hemorrhage and recurrent thrombo-embolism in two of the eight reported cases of idarucizumab-facilitated thrombolysis to date is nonetheless noteworthy.

Further studies are needed to evaluate the risks and benefits of idarucizumab-facilitated thrombolysis before this approach is universally adopted. Previously published cases have generally had good outcomes though this could in part reflect publication bias. The authors strongly recommend the establishment of an international clinical registry to monitor outcomes in idarucizumab-facilitated thrombolysis to ensure that this potentially invaluable therapy is safe and effective in clinical practice.

Figure 1 Adverse clinical outcome in two patients with idarucizumab-facilitated thrombolysis.

Case 1 presented with acute left tandem ICA-MCA occlusion as shown on non-contrast CT with hyperdense MCA sign (arrow) and on CTA (b). Day-1 post thrombolysis CT showed large left hemispheric infarct with significant hemorrhage (c & d). Case 2 presented with left hemiparesis with right frontal ischemic penumbra (arrow) on perfusion CT (e). Right frontal evolving infarct (arrow) was seen at 24-hours post-thrombolysis (f). Contralateral stroke recurrence developed at 30-hours with distal MCA hyperdense sign (arrow). Follow-up CT showed established left frontal infarct.

	Age; Gender	Country and Date of Publication	Comorbidities	Dabigatran dose and interval between dose and stroke onset	Infarct territory; symptoms, severity & radiological findings	Idarucizumab dosage and time interval between tPA and idarucizumab	Clinical outcome	Adverse effect
1	67yo; F	Germany ⁶ ; May 2016	NS	150mg BD; 4 hr	Right MCA; Hemiparesis; NIHSS 10; CTP deficit & M3 occlusion	5g IV; 5 minutes	Motor deficit improved Discharged to rehabilitation;	Nil
2	76yo; M	Germany ³ ; June 2016	Hypertension, DM	110mg BD; 1 hr	Left MCA; Hemiparesis, global dysphasia, neglect; NIHSS 11	5g IV; Immediate	NIHSS 3 at 24 hr, NIHSS 1 at day 7; Discharged to rehabilitation	Nil
3	75yo; F	Germany ⁷ ; June 2016	Hypertension, Ulcerative colitis	110mg BD; NS	Left PCA; Hemiparesis, gaze deviation, hemianopia; NIHSS 7	NS	NIHSS 18 at discharge to rehabilitation	Aspiration pneumonia
4	76yo; F	Belgium ⁸ ; Sept 2016	Hypertension, Temporal arteritis	110mg BD; 9 hr	Right PCA; Hemiparesis, dysarthria; NIHSS 11; CTP deficit	5g IV; Immediately	NIHSS 3 at day 1, NIHSS 1 at day 7	Nil
5	68yo; M	Austria ⁹ ; Sept 2016	Overweight, Stroke, Renal impairment	110mg BD; 50 min	Right PCA; Hemianopia, headache, dizziness; NIHSS 3; DWI/FLAIR mismatch	Two 2.5g IV boluses; 15 min	NIHSS 3; Hemianopia improved at discharge	Nil
6	75yo; M	Germany ¹⁰ ; Sept 2016	Cardiac failure, Hypertension, DM, Stroke, Epilepsy, Vascular disease, Hepatic and renal impairment	110mg BD; 9.5 hr	Left MCA; NIHSS 5;	Two 2.5g IV boluses; NS	Symptoms resolved at 1 hr	Nil

Table 1 Summary of six reported cases to date.

Index: yo = years-old; M = Male; F = Female; NS = Not stated; DM = Diabetes Mellitus; BD = Twice daily; hr = hours; min = minutes; s = seconds; NIHSS = National Institute of Health Stroke Scale; MCA = Middle Cerebral Artery; PCA = Posterior Cerebral Artery; CTP = Computer Tomography Perfusion; DWI = Diffusion Weighted Imaging; FLAIR = Fluid-attenuated Inversion Recovery; M3 = Cortical branch of Middle Cerebral Artery; tPA = tissue plasminogen activator; g = gram; IV = Intravenous.

Consent for case reports: Written consents were obtained by patient and families

Conflict of Interest: The authors declare that they have no conflict of interest

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