

Emergency Lumbar Puncture for Suspected Meningitis after Dabigatran Reversal with Idarucizumab: A Case Report

Agosti S^{1*}, Casalino L¹, Daffonchio A², Arena L³, Celli L³ and Rota E³

¹Cardiology Unit, San Giacomo Hospital, Novi Ligure, Alessandria, Italy

²Neurology Unit, San Giacomo Hospital, Novi Ligure, Alessandria, Italy

³Internal Medicine Unit, San Giacomo Hospital, Novi Ligure, Alessandria, Italy

Abstract

Idarucizumab is a monoclonal antibody which has been shown to be effective for rapid, durable, and safe reversal of the anticoagulant effect of dabigatran. We will describe herein the third case reported so far on the use of idarucizumab in a patient on dabigatran for nonvalvular atrial fibrillation and an indication for emergency lumbar puncture for suspected meningitis.

Keywords: Dabigatran; Direct oral anticoagulants; Idarucizumab; Lumbar puncture

Introduction

Current international guidelines recommend early lumbar puncture (LP) in patients with suspected acute bacterial meningitis. LP is an invasive procedure and is contraindicated in patients on warfarin or direct oral anticoagulants (DOACs), unless a reversal of the anticoagulant effect has been achieved, due to the increased periprocedural hemorrhagic risk.

Discontinuation and management of DOACs for emergency procedures pose a challenge [1], where withdrawal rules and bridging therapy have been questioned in relation to the clinical scenario.

Recently, the first reversal agent for a DOAC-idarucizumab-has been shown to be effective for a rapid, durable and safe reversal of the anticoagulant effect of dabigatran in patients developing life-threatening bleeding or undergoing urgent procedures [2].

Case Report

An 82-year-old man presented to our emergency department with a temperature of 39°C (102°F) and progressive impairment of consciousness up to coma, associated with high white blood cell count (15,000/ml) and increased serum C-reactive protein (27.2 mg/dl) and procalcitonin (2.1 ng/ml) levels. Creatinine clearance was 72 ml/min.

His general condition was poor, with pressure ulcers on the sacrum and heels. He had a history of type 2 diabetes mellitus, permanent atrial fibrillation, chronic ischemic heart disease, and had previously been implanted with a pacemaker. A previous computed tomography (CT) scan of the brain, performed one year earlier after a traumatic brain injury, had revealed signs of a left cerebellar ischemic stroke.

The patient was on twice daily medication of dabigatran 110 mg, metformin 850 mg, ranolazine 375 mg and bisoprolol 1.25 mg, and on daily doses of paroxetine 20 mg, digitalis 0.125 mg, canrenone 50 mg, transdermal nitroglycerin 5 mg, furosemide 25 mg and allopurinol 300 mg.

At neurological assessment, he was deeply obtunded, responding with facial grimacing to painful stimulus (Glasgow Coma Scale 3), and showing neurological signs compatible with meningitis (neck stiffness with positive Kernig's and Brudzinski's signs). The urgent brain CT scan was unremarkable.

Due to the suspicion of meningitis, the patient was given an emergency indication for diagnostic LP, and in order to minimize the risk of spinal hematoma, it was decided to neutralize the anticoagulant activity of dabigatran (last intake 7 h previously) by administering

idarucizumab at 5 mg i.v. bolus. LP was performed ~15 min after idarucizumab administration, and no complications or bleeding events occurred during the procedure. The activated partial thromboplastin time (aPTT) was 49.8 sec (n.v. 20.0-29.6 sec) before idarucizumab administration and 28 sec the day after. Dabigatran was resumed 16 hrs after the procedure (earlier than 24 h, because of the high stroke risk, according to the CHADSVASC score of 7).

LP detected high protein levels (133 mg/dl; n.v.<50 mg/dl), low blood glucose levels (30 mg/dl, corresponding to 14% of blood sugar levels), in the presence of 33 cells (lymphocytes and granulocytes)/ μ l (n.v.<5). The nested multiple polymerase chain reaction assay of cerebrospinal fluid was negative for Herpes Virus, Enterovirus, Human Parechovirus, *Neisseria meningitidis*, *Escherichia coli*, *Listeria monocytogenes*, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Hemophilus influenzae* and *Cryptococcus neoformans*. In contrast, blood cultures were positive for penicillin-susceptible *Staphylococcus aureus*. Therefore, the patient was administered a combined antibiotic treatment with vancomycin, piperacillin-tazobactam and ceftriaxone.

Both echocardiography and chest X-ray were negative for endocarditis. Abdominal CT revealed signs of intestinal subocclusion with markedly distended loops of the large bowel, most likely due to paralytic ileus.

The patient died of septic shock 11 days after admission to hospital.

Discussion

Idarucizumab is the first reversal agent for a DOAC which allows highly effective and safe reversal of the anticoagulation effect of dabigatran in patients developing life-threatening bleeding or undergoing urgent procedures [2,3]. The effect of idarucizumab is extremely rapid and sustained for 12 hours, meaning that surgical

*Corresponding author: Sergio Agosti, Cardiology Unit, San Giacomo Hospital, Via E. Raggio 15067 Novi Ligure (AL), Italy, Tel: +39 348 7760927; E-mail: agostisergio@virgilio.it

Received March 03, 2018; Accepted April 07, 2018; Published April 13, 2018

Citation: Agosti S, Casalino L, Daffonchio A, Arena L, Celli L, et al. (2018) Emergency Lumbar Puncture for Suspected Meningitis after Dabigatran Reversal with Idarucizumab: A Case Report. J Clin Case Rep 8: 1103. doi: 10.4172/2165-7920.10001103

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procedures can be started shortly after administration. Provided that the risk of thrombosis outweighs the risk of bleeding, anticoagulant treatment should resume after surgery or invasive procedures once adequate hemostasis is restored. Evidence of a normal aPTT and thrombin time (TT) before surgery or an invasive procedure can help to confirm reversal. It is important to point out, however, that coagulation testing before the administration of idarucizumab is not essential in patients who have life-threatening bleeding or in whom urgent surgery is indicated. Although there are some data about a dissociation between the normalization of the coagulation profile and the establishment of effective hemostasis after the administration of idarucizumab at least in certain clinical settings, such as cerebral hemorrhage [4], on the contrary our case suggests that idarucizumab is an effective and safe reversal of the anticoagulation effect of dabigatran in patients that are undergoing urgent procedures.

To the best of our knowledge, only two previous cases on the use of idarucizumab have been reported in patients taking dabigatran with an emergency indication for LP due to a suspicion of meningitis, with similar clinical setting, timing/mode of idarucizumab administration and periprocedural outcomes, with normalization of coagulation tests and no bleeding complications. Ours is the third such case. In the first case, an 81-year-old woman was hospitalized due to somnolence and meningeal symptoms [5,6]. The patient was on dabigatran 110 mg BID due to non-valvular atrial fibrillation and also had diabetes mellitus and a history of intracranial hemorrhage. C-reactive protein levels were 4.4 mg/dL, leading to suspicion of neuroinfection. Because the previous dabigatran administration was in the morning and coagulation tests were prolonged, idarucizumab (5 g i.v.) was administered. LP was performed 30 min later. There were no bleeding complications and no neuroinfection: the patient actually had opiate toxicity. Dabigatran treatment was reinitiated the next day. The second case was an 85-year-old man with suspected infective cerebral disease [6]. The patient was on dabigatran 110 mg BID because of non-valvular atrial fibrillation and also had hypertension, hyperlipidemia and chronic renal insufficiency. The time of last dabigatran intake was unknown. Coagulation tests were prolonged. Differential diagnoses included stroke with infective disease and infective cerebral disease. Emergency LP was performed, and the patient was injected with idarucizumab (5 g i.v.). Coagulation tests rapidly normalized and the patient had no bleeding complications. Further investigations revealed very mild pleocytosis, a subacute middle cerebral artery infarction, a high grade left-sided proximal internal carotid artery stenosis, and acute laryngitis. Carotid endarterectomy

was performed because of the high-grade stenosis and the patient was given antibiotics because of the laryngitis.

Although LP is essential for emergency cerebrospinal fluid analysis in cases of suspected meningitis, this diagnostic procedure may be challenging in patients on DOACs [7]. The availability of the dabigatran antidote idarucizumab is of paramount importance for the practical management of these specific clinical scenarios.

LP was performed in our patient just 15 minutes after idarucizumab administration; aPTT was almost halved after dabigatran antagonization; no early or late thrombotic complications occurred and DOAC therapy could be started again 16 hours after the procedure, as soon as it was deemed appropriate, earlier than the usually recommended 24 hours [1].

LP played a key role in the diagnosis of meningoencephalitis and prompted antibiotic treatment, even though it was not possible to halt the progression of the severe clinical picture.

Conclusion

In conclusion, our case further supports the use of the reversal agent idarucizumab for the periprocedural management of patients on anticoagulation with dabigatran in emergency clinical settings.

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