




EXCEPTIONAL CASE

Idarucizumab for the treatment of dabigatran-related nephropathy

Ammar Alsamarrai ¹, Nicola Eaddy² and Elizabeth Curry¹¹Department of Renal Medicine, Auckland City Hospital, Auckland, New Zealand and ²Department of Haematology, Auckland City Hospital, Auckland, New ZealandCorrespondence to: Ammar Alsamarrai; E-mail: Ammaral@adhb.govt.nz

ABSTRACT

Anticoagulant-related nephropathy (ARN) is a clinical syndrome of acute kidney injury in patients taking vitamin K antagonists or direct oral anticoagulants. It is associated with increased mortality and there is no specific treatment. We report the case of a 78-year-old man on dabigatran who developed macroscopic haematuria and acute kidney injury 2 weeks after mitral valve repair, reaching a peak creatinine of 415 $\mu\text{mol/L}$ from a normal baseline, which was successfully treated with one course of idarucizumab. This case illustrates the efficacy of an anticoagulant reversal agent for the treatment of ARN.

Keywords: acute kidney injury, anticoagulant-related nephropathy, dabigatran nephropathy, direct oral anticoagulant, idarucizumab

BACKGROUND

Anticoagulant-related nephropathy (ARN) is a clinical syndrome of acute kidney injury due to glomerular haemorrhage, tubular obstruction and tubular injury and historically it was described in patients with supratherapeutic levels of warfarin [1]. The direct oral anticoagulants (DOACs) have more favourable safety profiles than warfarin and lower rates of major haemorrhage, as well as targeted and effective reversal agents. We report the clinical outcome of a patient diagnosed empirically with dabigatran-related nephropathy that was successfully treated with the reversal agent idarucizumab.

CASE REPORT

A 78-year-old New Zealand European male presented to the hospital with lower back pain, fevers and generalized malaise. He had a background history of atrial fibrillation, mitral valve

prolapse and fusion of the lower lumbar vertebral bodies and was usually on dabigatran 110 mg twice daily, flecainide and cilazapril. His examination was notable for signs of heart failure, and two sets of blood cultures taken at the time of admission grew *Enterococcus faecalis*. Due to suspicion of endocarditis and spinal infection, he was treated with intravenous amoxicillin, ceftriaxone and gentamicin. Echocardiography demonstrated severe mitral regurgitation and magnetic resonance imaging of the lumbar spine was suggestive of discitis. He underwent urgent mitral valve repair and had an uncomplicated operation and immediate post-operative course. He remained in the intensive care unit for 4 days. His creatinine throughout this time was in the range of 70–80 $\mu\text{mol/L}$.

On Day 9 post-operatively, he developed atrial fibrillation with rapid ventricular rate and was commenced on regular amiodarone, which is known to increase the plasma concentration of dabigatran. On Day 14 post-operatively, he suddenly developed macroscopic haematuria with an associated increase in

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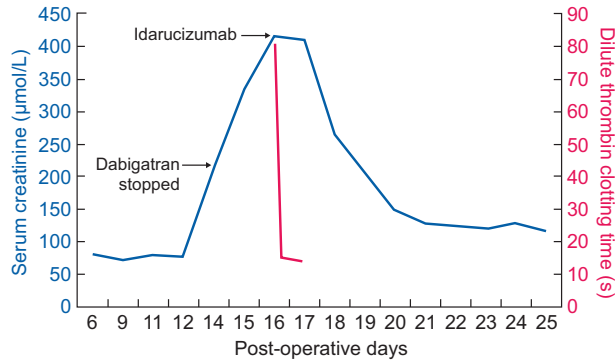


FIGURE 1: Time course in the treatment of dabigatran-related nephropathy with idarucizumab.

serum creatinine to a peak of 415 µmol/L over 3 days (Figure 1). Urine microscopy was not possible due to heavy blood staining, although no microorganism was grown on urine culture. Renal tract ultrasound showed left-sided pelvicaliceal and proximal ureteric dilatation and a non-distended urinary bladder. Non-contrast computed tomography imaging was limited by metal-ware artefact but did not show a definite obstructing cause for the left renal tract dilatation. Throughout this time he maintained a urine output in the range of 1500–2000 mL/day.

Acute interstitial nephritis (AIN) due to amoxicillin was considered; however, there was no recovery of renal function when this was discontinued and the rate of increase in creatinine was thought to be unusual for AIN. Furthermore, this would not have accounted for the gross haematuria. Serum complement, viral hepatitis serology, human immunodeficiency virus screen, antineutrophil cytoplasmic antibodies, antinuclear antibodies and streptococcal serology were all unremarkable. Renal biopsy was considered; however, this was not pursued due to the risk of procedural complications (from recent administration of dabigatran).

Further scrutiny of the medical history revealed an episode 6 years prior of macroscopic haematuria when on warfarin, for which no cause was found despite renal tract imaging (which demonstrated bilateral ureteric jets, indicating bilaterally functioning kidneys) and flexible cystoscopy. Despite withholding dabigatran for 2 days, the dilute thrombin clotting time was significantly elevated (>80 s), indicating active anticoagulant effect, and the creatinine remained elevated. A presumptive diagnosis of ARN due to dabigatran was made and 5 g of idarucizumab was administered. After 2 days there was an improvement in his serum creatinine to 265 µmol/L, with subsequent improvement to a new baseline of 120 µmol/L over 5 days. There was also the immediate resolution of the macroscopic haematuria, although there was a polyuric phase in the recovery. He was successfully discharged home 1 month after the operation and the serum creatinine returned to normal after 2 months.

Of note, as renal biopsy was not undertaken in this case, the diagnosis of ARN was empiric and we cannot exclude that spontaneous recovery of renal function occurred.

DISCUSSION

The prevalence of ARN ranges between 19% and 63% of patients treated with warfarin, and it is associated with a significantly increased 5-year mortality rate relative risk of death 1.91 (95% confidence interval 1.22–3.0) [2]. While there have only been reports of DOAC-related nephropathy, a recent pooled analysis

Table 1. List of common oral anticoagulants and their reversal agents

Anticoagulant	Reversal agent
Warfarin	Prothrombin complex concentrate Vitamin K
Dabigatran	Idarucizumab
Rivaroxaban	Andexanet alfa
Apixaban	Andexanet alfa
Edoxaban	Ciraparantag ^a

^aIn preclinical trials.

suggested that DOACs (except for apixaban) have significantly lower rates of any adverse renal outcome compared with warfarin [3]. While there is no specific treatment for ARN, anticoagulant reversal agents have provided a novel therapeutic option (Table 1). This premise was successfully tested by Awesat *et al.* [4] and, to our knowledge, this is the second report in the literature of using idarucizumab to treat dabigatran-related nephropathy. The importance of this observation is 3-fold. First, dabigatran-related nephropathy is a reversible process and should be managed promptly to avoid permanent renal damage. Second, treatment with idarucizumab may obviate the need for dialysis and should be considered early in cases of suspected dabigatran-related nephropathy. Third, the principle of using reversal agents to treat ARN could be considered with other anticoagulants. To our knowledge, there has not been any report in the literature of using human prothrombin complex in cases of warfarin-related nephropathy, and the development of newer reversal agents opens the possibility of an effective treatment option for ARN. It should be noted that the reversal of anticoagulation carries the risk of thrombosis, usually due to the underlying prothrombotic state, and this needs to be balanced against any potential benefits of such a decision.

PATIENT CONSENT

The authors obtained informed consent from the patient to publish this case in a medical journal.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, except in abstract form.

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