




EXCEPTIONAL CASE

Dabigatran overload in acute kidney injury: haemodialysis or idarucizumab? A case report and proposal for a decisional algorithm

Andrea Galassi^{1,2}, Gianmarco Podda^{1,3}, Paola Monciino^{1,2}, Andrea Stucchi², Alberto Del Nero⁴ and Mario Cozzolino ⁵

¹Renal Division, Department of Health Sciences, University of Milan, San Paolo Hospital, Milan, Italy, ²Renal & Dialysis Unit, San Paolo Hospital, ASST Santi Paolo e Carlo, Milano, Italy, ³Internal Medicine Unit III, San Paolo Hospital, ASST Santi Paolo e Carlo, Milano, Italy, ⁴Urology Unit, San Paolo Hospital, ASST Santi Paolo e Carlo, Milan, Italy and ⁵Department of Health Sciences, University of Milan Ringgold Standard Institution, Milano, Italy

Correspondence to: Andrea Galassi; E-mail: andrea.galassi@asst-santipaolocarlo.it; Twitter handle: @MarioCozzolin19

ABSTRACT

Dabigatran overload has been reported in acute kidney injury (AKI), leading to occasional major bleeding. Haemodialysis (HD) was the method used for reversing dabigatran anticoagulant effects before the approval of idarucizumab, which is now indicated for dabigatran reversal in major bleeding or surgical emergencies. There have been reports of rebound of dabigatran levels following idarucizumab administration in AKI, requiring HD to achieve effective dabigatran clearance. However, a decisional algorithm to individualize treatments for dabigatran overload seems lacking. We present a case of dabigatran accumulation in obstructive AKI with minor bleeding that was successfully treated with HD and tranexamic acid without using idarucizumab, and propose a decision-making algorithm including different pathways in the management of suspected dabigatran overload in AKI.

Keywords: acute kidney injury, dabigatran, decision algorithm, dialysis, idarucizumab

INTRODUCTION

Dabigatran is a direct thrombin inhibitor, used in the prevention of stroke in atrial fibrillation (AF) and in the management and prevention of venous thromboembolism. Dabigatran is mainly eliminated by renal excretion, and hence it is contraindicated in patients with creatinine clearance (CrCl) of <30 mL/min [1]. Dabigatran increases the risk for bleeding, particularly in acute kidney injury (AKI) [2].

Before 2015, haemodialysis (HD) was unique rescue therapy for urgent dabigatran reversal, e.g. in the setting of bleeding and/or emergent surgery and/or dabigatran overload in AKI, since dabigatran has a low molecular weight and weak protein-binding properties [3].

In 2015, idarucizumab, a humanized monoclonal antibody directed against free and thrombin-bound dabigatran, was approved to address the need for an agent that can reverse dabigatran's anticoagulant effects [4]. Rebound in circulating

Received: 8.12.2019; Editorial decision: 7.1.2020

© The Author(s) 2020. Published by Oxford University Press on behalf of ERA-EDTA.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

dabigatran levels after idarucizumab administration was reported in AKI, conditioning refractory anticoagulation [2], requiring HD for dabigatran clearance [2, 5]. Several factors may account for the rebound increases in dabigatran levels in AKI, including redistribution of dabigatran from the extravascular to vascular space, obesity and protracted dabigatran assumption in, often asymptomatic, renal function decline [2].

A systematic approach should guide the decision-making process to rapidly determine the efficacy of idarucizumab and HD in individual patients, leading to cost-effective treatment of dabigatran overload and its complications in AKI.

We report a case of dabigatran overload with minor bleeding, as a result of obstructive AKI, which was successfully treated with six HD sessions and tranexamic acid, without using idarucizumab. We therefore propose an algorithm

for managing patients with dabigatran overload in AKI (Figure 1).

CASE PRESENTATION

An 82-year-old man with a ‘laboratory’ diagnosis of AKI [serum creatinine (sCr) 14 mg/dL] was admitted to the emergency room. His clinical history included AF (CHA2DS2-VASc = 3), prostatic adenocarcinoma, chronic kidney disease stage G3b (sCr 1.9 mg/dL, Cockcroft–Gault estimated CrCl 30 mL/min), arterial hypertension and chronic anaemia [haemoglobin (Hb) 11.6 g/dL 2 months earlier]. He received chronic treatment with dabigatran 100 mg twice daily, digoxin, hydrochlorothiazide, olmesartan, bisoprolol, febuxostat and dutasteride. Biochemistry investigations on admission confirmed AKI, acute anaemia

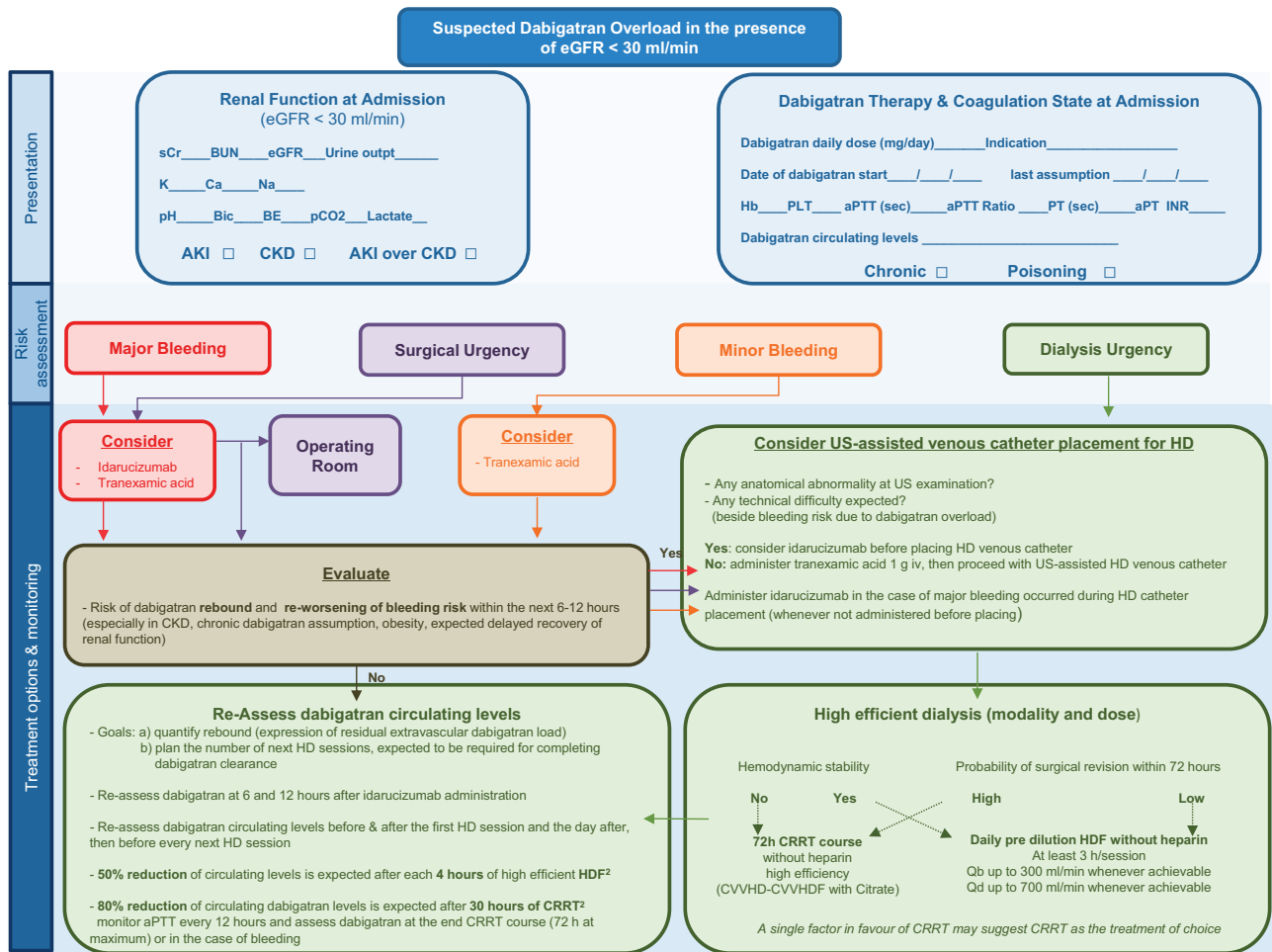


FIGURE 1: Decision-making algorithm including different pathways in the management of suspected dabigatran overload in AKI. Dabigatran overload should be suspected in patients treated with dabigatran with an eGFR < 30 mL/min. The algorithm comprises three major steps: (i) ‘Presentation’: two boxes summarize essential data on renal function, electrolyte levels, dabigatran treatment, dabigatran circulating levels, coagulation state and anaemia; (ii) ‘Risk assessment’: this includes four conditions that define the risk severity related to dabigatran overload; (iii) ‘Treatment options & monitoring’: in the presence of major bleeding (red pathway) or surgical urgency (violet pathway), idarucizumab and tranexamic acid should be considered as first-choice treatment, following evaluation of factors favouring dabigatran rebound with refractory anticoagulation (brown box) that may require HD within next 6–12 h (green pathway); in the presence of minor bleeding (orange pathway), treatment with tranexamic acid may be sufficient, without the need for idarucizumab, but still requiring assessment of factors favouring dabigatran rebound with refractory anticoagulation requiring HD (brown box); dialysis urgency (green pathway), due to severity of AKI and related complications, will require venous dialysis catheter placement; suggestions related to dialysis catheter placement, choice of dialysis technique, dialysis prescription and monitoring of dabigatran and coagulation profile are summarized in green boxes. aPTT, activated partial thromboplastin time; BE, base excess; Bic, serum bicarbonate; Ca, serum calcium; CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; INR, international normalized ratio; K, serum potassium; Na, serum sodium; PLT, platelet count; PT, prothrombin time; Qb, dialysis blood flow rate; Qd, dialysate flow rate; Ratio, aPTT ratio.

with signs of anticoagulation (Supplementary data, Figure S1) and mild metabolic acidosis with normokalaemia (bicarbonate 19 mmol/L, lactate 1.23 mmol/L, potassium 4.8 mmol/L). Ultrasound (US) examination revealed bilateral hydronephrosis with stenotic terminal ureters. Dabigatran, digoxin and olmesartan were discontinued. The patient was transferred to the Medicine Unit, and was referred for bilateral urostomy placement after dabigatran washout. Within the next 48 h, epistaxis with worsening anaemia (Hb 7.5 g/dL) occurred, requiring blood transfusion, intravenous (IV) tranexamic acid and nasal tamponade. Two days post-treatment, the patient was asymptomatic, showing no signs of heart failure, with a diuresis rate of 0.5 L/24 h achieved with IV furosemide. Dabigatran levels were high (666 ng/mL), whereas other biochemical parameters remained mainly unchanged (Supplementary data, Figure S1). Following a multidisciplinary discussion between the nephrologist and the internist, HD treatment was preferred for removal of dabigatran before urological intervention, thus circumventing the need for idarucizumab in case of major bleeding, due to: (i) the high risk for dabigatran rebound after idarucizumab administration in severe AKI; (ii) the patient's lengthy exposure to dabigatran; (iii) the absence of major uncontrolled bleeding; and (iv) the absence of other surgical emergencies. Bleeding risk related to US-guided placement of a temporary dialysis catheter in the femoral vein was considered acceptable without the need for idarucizumab, based on the absence of increased anatomical risks at US evaluation and with the expectation of effective primary haemostasis achievable with IV tranexamic acid administration if required. A temporary dialysis catheter was placed in the femoral vein without complications. On Day 2 post-catheter placement, 3-h haemodiafiltration (HDF) without heparin was performed, leading to 50% reduction in dabigatran levels (366 ng/mL). On Day 3, dabigatran levels were still elevated (355 ng/mL). Five further HDF sessions were undertaken for adequate dabigatran clearance (35 ng/mL), which was achieved on Day 9. Bilateral urostomy placing was delayed on Day 10, due to restored diuresis and metabolic control as a result of HD treatment and complete dabigatran clearance achieved on Day 9 (Supplementary data, Figure S1). Calciparin was introduced on Day 11. The patient was discharged on Day 14 (sCr 3.6 mg/dL). Warfarin was commenced 1 month later. During the 4 months following discharge, the patient was readmitted three times to the urology unit for urostomy replacement (the left urostomy was not further replaced, due to resolved left hydronephrosis) and due to one episode of urinary infection. On Day 121, sCr returned to 1.9 mg/dL. The estimated cost related to treatment with HDF and tranexamic was €1860, compared with a cost of €4738 for two minimal doses of idarucizumab, which might have been inadequate for complete dabigatran clearance.

DISCUSSION

The present case highlights the following important points: (i) a one-size-fits-all approach may not be appropriate in terms of the efficacy and safety of interventions to treat dabigatran overload in AKI patients; (ii) a systematic algorithm for guiding an individualized approach is recommended (Figure 1); (iii) HD remains a strong treatment option for managing dabigatran overload in severe AKI, even in the era of idarucizumab; (iv) tranexamic acid is effective in controlling the bleeding risk of uncomplicated US-guided placement of venous femoral dialysis catheters in cases of dabigatran overload; and (v) daily HD or continuous renal replacement therapy may be required for effective dabigatran clearance in AKI, guided by continuous monitoring of dabigatran circulating levels.

PATIENT CONSENT

The patient and his family gave informed consent to publish this case.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest related to the present manuscript.

REFERENCES

1. Stangier J, Rathgen K, Stahle H et al. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel, single-centre study. *Clin Pharmacokinet* 2010; 49: 259–268
2. McBride L, Wang J, Ho P et al. Dabigatran toxicity in acute kidney injury: hemodialysis and idarucizumab required. *Kidney Int Rep* 2019; 4: 500–504
3. Singh T, Maw TT, Henry BL et al. Extracorporeal therapy for dabigatran removal in the treatment of acute bleeding: a single center experience. *Clin J Am Soc Nephrol* 2013; 8: 1533–1539
4. Pollack CV Jr, Reilly PA, van Ryn J et al. Idarucizumab for dabigatran reversal-full cohort analysis. *N Engl J Med* 2017; 377: 431–441
5. Marino KK, Santiago RA, Dew RB et al. Management of dabigatran-associated bleeding with two doses of idarucizumab plus hemodialysis. *Pharmacotherapy* 2016; 36: e160–e165