

Clinical Report

Venovenous haemodiafiltration for the management of dabigatran overdose in intensive care unit

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Abstract

Dabigatran is a direct thrombin inhibitor indicated for thromboembolism prophylaxis in patients with non-valvular atrial fibrillation. The procedure to manage dabigatran-associated haemorrhages is not well formalized. Conventional haemodialysis has been evaluated with good results. Patients with dabigatran-associated bleeding may be unstable and convective techniques like venovenous haemodiafiltration (HDF) can be interesting. We report the case of a 74-year-old, critically ill patient with haemorrhagic shock and dabigatran overexposure due to acute kidney injury. He underwent HDF and dabigatran blood concentrations decreased from 325.3 ng/mL to 160.5 ng/mL. We report here key pharmacokinetics parameters (half-life, extraction coefficient, clearance).

Keywords: dabigatran overexposure; haemodiafiltration; haemorrhagic shock; intensive care

Context

Dabigatran is a direct thrombin inhibitor indicated in prevention of thromboembolic disease in patients with non-valvular atrial fibrillation [1]. Contrary to vitamin K antagonists, no specific blood monitoring is recommended for dabigatran even if there is a real risk of accumulation in the case of renal impairment [2–4]. Importantly, there is no specific antidote of dabigatran. Presently, the procedure to reverse dabigatran in the case of life-threatening bleeding or in situations where urgent surgery is required is not well formalized. It is suggested to use procoagulant drugs [5, 6]. Additionally, based on the characteristics of dabigatran (small molecular weight of 630 Da and low binding to proteins, 30%), haemodialysis is proposed [7].

Previous studies have focused on removal of dabigatran using conventional haemodialysis, with good results [7–16]. Conventional dialysis usually means a diffusive method with high blood flow (~350 mL/min), arteriovenous fistula and high dialysate rate (~500 mL/min). Not rarely, patients with life-threatening bleeding need to be hospitalized in the intensive care unit (ICU) where conventional techniques are not always available. Furthermore, patients with massive bleeding can be haemodynamically unstable and conventional haemodialysis in this context may not be well tolerated. For these reasons, the use of convective-based renal replacement therapy (RRT) like haemodiafiltration (HDF) may have a place in the management of patients with undesirable blood concentration of dabigatran.

However, very few data exist on the ability of those techniques to efficiently remove dabigatran from blood [17].

We report here the case of a patient admitted to the ICU for life-threatening bleeding in the context of dabigatran overexposure managed by HDF.

Case report

A 74-year-old man was presented to the emergency department with epigastric pain, asthenia and drowsiness. He had a past medical history of chronic heart failure, chronic subdural haematoma, atrial fibrillation and chronic kidney disease stage 3b and received dabigatran 75 mg twice daily. He took his last dose of dabigatran 7 h before the admission. He was somnolent but arousable, confused with Glasgow Coma Scale 14, haemodynamically unstable with hypotension (95/51 mmHg), mottled skin and tachycardia (100 bpm). Mucocutaneous pallor was noted but without external bleeding. First biology results found anaemia with haemoglobin 7 g/dL (versus 11.5 g/dL two weeks before) and creatinine 276 µmol/L (versus 150 µmol/L usually) i.e. acute kidney injury stage 1 KDIGO. Plasma coagulation was abnormal with prothrombin ratio (PR) 28% and activated partial thromboplastin time (aPTT) 66 s. Blood dabigatran level was 534.9 ng/mL. Brain computed tomography found chronic subdural haematoma without acute bleeding. The patient received 3 packed red blood cells and 1000 mL of intravenous fluids (sodium

chloride 0.9%). Upper gastrointestinal endoscopy was realized, finding stomach ulcer with acute bleeding. He was treated by local epinephrine injection and clipping with good efficiency. Continuous infusion by proton pump inhibitor was started (omeprazole 8 mg/h). He did not receive procoagulants drugs. The patient was hospitalized in ICU for RRT.

In ICU, a dialysis catheter (Blue FlexTip Catheter, 2 lumen, 16 cm, 12 Fr - ARROW®) was inserted in the right internal jugular vein. The patient was started on 4 h of HDF on PRISMA FLEX System (GAMBRO®) with a high-flux dialysis filter (Multiflow 60 AN69HF 0.60 m² polyacrylonitrile hollow-fibre membrane). The blood (Qb), dialysate (Qd) and ultrafiltration (Quf) flow rates were 200 mL/min, 1 L/h and 3 L/h, respectively. Substitution fluids were delivered in predilution (1 L/h) and in postdilution (2 L/h) with zero net ultrafiltration. Dabigatran levels were sampled every 20 min in blood (inlet line) and effluent (ultrafiltration and dialysate volume collected every 20 min). Dabigatran level was measured by validated liquid chromatography tandem mass spectrometry method. The patient remained awake and alert for the entire session, without external bleeding. Diuresis was 250 mL on 8 h with residual clearance of creatinine measured at 14 mL/min. Dabigatran plasma concentration was 325.3 ng/mL at the beginning of RRT. It decreased gradually during the session to reach 160.5 ng/mL after 4 h (Figure 1). Decrease of dabigatran during HDF was of 25% at 2 h and 51% at 4 h. Conversely, the effluent level of dabigatran increased to reach 138.5 ng/mL at the end of the session. In parallel, aPTT decreased from 180 s at the initiation of HDF to 57.8 s 4 h after the session and PR increased from 30 to 41%. The patient did not receive any drugs that could have interfered with clotting time.

Mean haemodiafiltration clearance of dabigatran (Cl(hdf)) was 48 mL/min. Cl(hdf) was measured every 20 min using the recovery method according to the following equation $Cl(hdf) = EV/P$ where E = effluent concentration of dabigatran, V = effluent rate and P = dabigatran plasma concentration. The half-life of dabigatran was 4.8 h. Only the terminal half-life was determined according to the following equation $T_{1/2} = \ln(2)/\lambda(z)$ where $\lambda(z)$ is the slope of the terminal portion of the log transform concentrations versus time. This was obtained by unweighted linear regression of at least three concentrations.

A rebound of concentrations of dabigatran was observed with a plasma level at 195.7 ng/mL 2 h after the end of the HDF session. Six hours after the HDF session, dabigatran concentration decreases to reach 11 ng/mL probably due to renal recovery. Because of renal recovery, clotting time improvement and decrease of dabigatran levels, no other dialysis session was realized.

The following day, haemoglobin was 8.6 g/dL. Control endoscopy was realized with a new clipping because of minimal bleeding. Renal function recovered with serum creatinine 168 µmol/L. Coagulation parameters continued to improve with PR 76% and aPTT 37 s at the patient's discharge. After cardiologic consultation, dabigatran was discontinued, replaced by aspirin because of a major risk of bleeding compared with the thromboembolic risk. The patient was discharged to home after 8 days.

Discussion

This case report focused on the interest of convective-based RRT in dabigatran-associated bleeding. In our

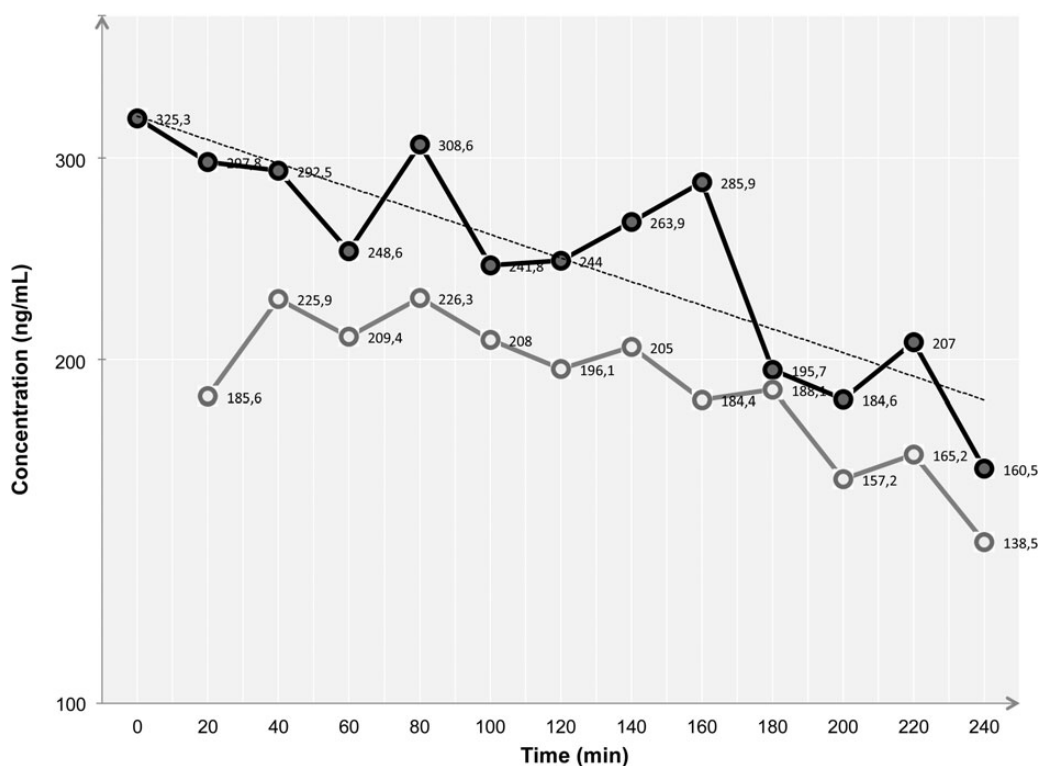


Fig. 1. Plasma and effluent dabigatran during HDF session. Black line represents dabigatran plasma concentrations; grey line represents dabigatran effluent concentration.

report, dabigatran blood level decreased from 325.3 to 160.5 ng/mL with a 4-h session of HDF equivalent to a decrease of 51% of dabigatran. This correlated with clotting time improvement. Dabigatran half-life during HDF session was 4.8 h. This figure has to be compared with an expected half-life of 28 h in this patient with glomerular filtration rate (GFR) below 30 mL/min [8]. Thus, the half-life during HDF session is <25% of the half-life off therapy which by definition confirms that dabigatran is effectively removed by HDF [18].

Several studies have previously reported the efficacy of haemodialysis techniques to clear dabigatran in different situations. Stangier *et al.* [8] found an extraction coefficient of dabigatran after 4 h of conventional haemodialysis at 68%, and Khadzhyrov *et al.* [9] reported extraction ratios >45%. Other cases have been reported with comparable results [11–16]. More recently, Singh *et al.* [12] published on their experience of five cases of acute bleeding associated to dabigatran. All patients received conventional haemodialysis with a decrease of dabigatran ranging from 52 to 77%. In his study, an additional RRT session because of a rebound of dabigatran concentrations was performed using continuous venovenous haemodiafiltration (CVVHDF) apparently with a good result but very few data are given. Regarding the efficacy of convective techniques, Chiew *et al.* reported on a 66-year-old man treated by 32 h of CVVHDF for dabigatran overdose. They found a mean extraction ratio of 0.2% and a mean dabigatran clearance of 58.1 mL/min using the recovery method [17].

This case report is a prototype of a patient requiring intensive care, with acute bleeding due to dabigatran overdose. Importantly, we provide here full pharmacokinetic analyses allowing an evaluation of key pharmacokinetic parameters (clearance, half-life).

Our work has other limitations. Decrease of dabigatran (51%) is less important than when conventional dialysis is used (50–80%), probably because of a low dialysate flow rate (1 L/h) and the small surface area of the filter (0.6 square metre). The absence of urine samples did not allow a direct evaluation of renal clearance of dabigatran but as the patient was oliguric we believed that renal excretion of dabigatran was negligible. The difference between dabigatran levels at the admission (534.9 ng/mL) and at the initiation of HDF (325.3 ng/mL) has probably more to do with haemodilution than renal excretion since the patient received three packed red blood cells and 1000 mL of saline solution before the beginning of HDF. The fact that the drug was not at steady-state when dialysis was started and the large distribution volume of dabigatran (70%) [7] can explain the relative increase of blood dabigatran concentrations during HDF session. Although thrombin time (TT) assay is the best test to assess dabigatran activity, it was not available in the emergency ward in our hospital. However, aPTT can be used for a qualitative assessment of dabigatran exposure, and some authors described a good correlation between aPTT and dabigatran concentrations [12].

In conclusion, this case report suggests that HDF may be an efficient approach for dabigatran removal and can be performed in the case of unstable, critically ill patients with dabigatran overexposure.

Conflict of interest statement. None declared.

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