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Dabigatran-associated subdural hemorrhage: using thromboelastography (TEG®) to guide decision-making

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Abstract Novel oral anticoagulants present challenges and uncertainties in the management of hemorrhagic emergencies. An 84-year-old man taking dabigatran presented with a subdural hematoma requiring neurosurgical intervention. Routine coagulation assays were prolonged at admission and following administration of Factor VIII Inhibitor Bypassing Activity (FEIBA). Thromboelastography (TEG®) was utilized to assess clot dynamics prior to placement of a subdural drain, which was safely inserted despite a prolonged thrombin time (TT). Exclusive reliance on the TT may delay necessary interventions. TEG® may be a valuable tool to investigate hemostasis in patients on dabigatran requiring emergent procedures.

Keywords Dabigatran · Intracranial hemorrhage · Thromboelastography · Prothrombin complex concentrates · FEIBA

Introduction

Dabigatran (Pradaxa®) is a direct inhibitor of both circulating and clot-associated thrombin [1]. Routine coagulation monitoring is not recommended; dabigatran possesses predictable pharmacokinetic properties with a wide therapeutic index. However, it presents new uncertainties during the management of hemorrhagic complications, particularly the lack of a rapid assay to quantify the degree of anticoagulation and the absence of a proven antidote [2].

Case report

An 84 year-old man presented to the hospital with bilateral frontal headache, confusion, and left lower extremity paresis. He was on dabigatran, with the last known ingestion 18 h prior to presentation. Head computed tomography (CT) revealed a 3 cm holohemispheric subacute subdural hematoma (SDH) with 1.5 cm midline shift and uncal herniation (Fig. 1a, b). Admission labs were: serum creatinine 1.3 mg/dL (reference range 0.4–1 mg/dL), activated partial thromboplastin time (aPTT) 41 s (23–35 s), prothrombin time (PT) 15.8 s (12–15 s), thrombin time (TT) >50 s (16.2–19.6 s) with normal fibrinogen and platelets (306 mg/dL and 197 K/mm^3, respectively).

Anticoagulation reversal was necessary for insertion of a subdural drain. Factor VIII Inhibitor Bypassing Activity (FEIBA) was administered at a dose of 3,036 units (43 units/kg). A repeat TT remained >50 s, and it was deemed unsafe to insert the drain given persistent anticoagulation. The patient remained confused with only a slight decrease in alertness over the following 8 h, at which time coagulation parameters were repeated and remained prolonged: aPTT 36.5 s and TT >50 s. A second dose of FEIBA, 3,489 units (50 units/kg), was administered. TT remained >50 s, and drain insertion was again delayed. The patient became progressively more lethargic over the next 4 h. An intrinsically kaolin-activated thrombelastography

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(TEG®) revealed an R-time of 4 min (reference range 5–10 min), K-time of 1.6 min (1–3 min), α angle of 68.8° (53°–72°), and MA of 58.9 mm (50–70 mm) (Fig. 2). At this time, the aPTT had normalized to 29.4 s, but the TT remained prolonged at 48 s (Fig. 3). A Subdural Evacuating Port System (SEPS®) was safely inserted, with a repeat head CT revealing a decrease in the SDH to 1.1 cm and midline shift to 0.5 cm (Fig. 1c, d). The patient's mental status and lower extremity paresis improved markedly over the subsequent 48 h, and he was discharged at his baseline.

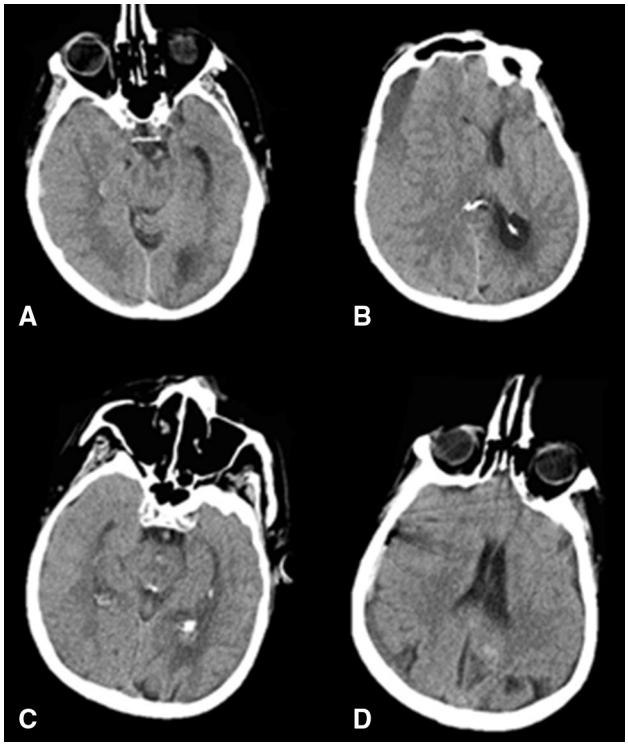

Fig. 1 Head CT pre-procedure revealing uncal herniation **a** and extra-axial blood collection with mass effect and midline shift **b**, and head CT post-procedure showing resolution of uncal herniation **c** and decreased blood collection and mass effect **d**

Discussion

Dabigatran is superior to warfarin for preventing thromboembolism in patients with non-valvular atrial fibrillation and causes fewer intracranial hemorrhages [1]. However, when reversal is required, little data is available to guide clinical decisions. Our patient did not have an acute bleed but did require anticoagulation reversal for neurosurgical management of a symptomatic SDH. It is common practice to perform neurosurgical interventions in patients with presumed low levels of anticoagulation (e.g. vitamin K antagonist with INR $\leq$ 1.4). At present, there is no equivalent measure for dabigatran. Drain insertion was delayed twice due to uncertainty about the degree of anticoagulation. A rapid assay to quantify dabigatran's effect on hemostasis is not validated or readily available in

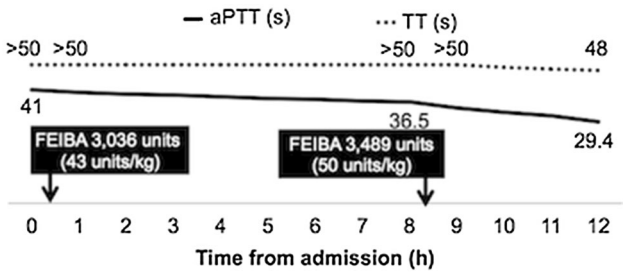

Fig. 3 Course of product administration and coagulation assay response

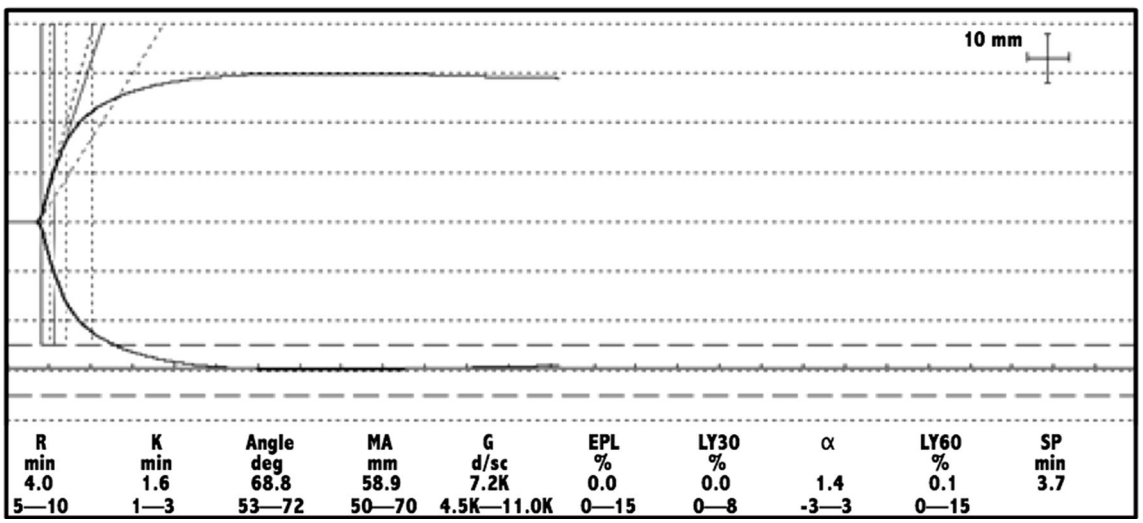

Fig. 2 TEG® tracing

clinical practice [1, 2] Conventional clot-based assays, aPTT and TT, display linear prolongation within published therapeutic serum dabigatran concentrations [1, 2]. However, only TT, not aPTT, has a high sensitivity for drug detection at concentrations below the reported therapeutic trough concentrations [2]. The presence or degree of prolongation is not validated as a risk predictor for further hemorrhagic complications. Nevertheless, it has been suggested that a normal TT is optimal prior to performing a high risk procedure [1]. However, the high degree of sensitivity may be prohibitive as seen in this patient whose TT remained significantly prolonged 36 h from the last dabigatran ingestion. Unlike conventional coagulation assays, which terminate on initial fibrin gel formation, TEG® allows monitoring for all phases of in vivo hemostasis including clot development, strength, and stabilization. The reported parameters are as follows: R-time (time to initial fibrin formation), K-time (time from initial fibrin formation to 20 mm of clot firmness), α angle (rate of clot formation) and MA (absolute strength of the clot) [3]. The evidence for the sensitivity and utility of TEG® to monitor direct thrombin inhibitors (DTI's) is limited, with no documented correlation to risk of bleeding. However, they are expected to prolong both the R and K-time, with modest reduction in the MA [4–6]. An intrinsically-activated (rather than a rapid extrinsically-activated) TEG® may provide additional insight on global hemostasis when low levels of dabigatran are anticipated. A rapid-TEG®, which is activated by an abundance of tissue factor, may enhance the production of factor VII, therefore overcoming DTI inhibition and normalizing TEG® parameters [7, 8].

In addition to quantifying the degree of anticoagulation, another challenge is formulating a strategy to effectively reverse dabigatran. The half-life is 12–17 h with 80 % renal excretion [1]. In this elderly patient with an elevated serum creatinine and systolic heart failure (ejection fraction 30 %), the half-life was likely prolonged. Although high-flux hemodialysis can eliminate the drug, it was not employed due to concerns for adverse intracranial volume-pressure alterations and potential complications of placing a large bore dialysis catheter in an unstable, anticoagulated patient [1, 9]. Thus, blood products were considered as an alternative. In human volunteers anticoagulated with dabigatran, FEIBA, which is an activated four factor prothrombin complex concentrate, is proposed to be the most effective reversal agent given its impact on thrombin generation kinetics [10]. However, the correction of clot-based laboratory assays, TT and aPTT, is negligible, and the clinical effectiveness is indefinite [10, 11]. A single case of a patient on dabigatran with a transseptal perforation reported that FEIBA did not reverse the TT but did quickly and effectively control bleeding [11]. The therapeutic impact of FEIBA in our case is uncertain. It is possible that it may have reduced the risk of spontaneous or procedure-related SDH, but considering the overall time course of the case, it is possible that the patient naturally eliminated adequate dabigatran to allow for normal clot formation. Demonstrating normalization of TEG® by performing the assay shortly preceding and following administration of FEIBA or other blood products may assist in delineating the role of these interventions. However, caution during interpretation is warranted as FEIBA may normalize TEG® parameters via a nonphysiologic stimulation of coagulation, with the impact of in vivo hemostasis remaining unknown [12].

In summary, reliance on a slightly prolonged aPTT and considerably prolonged TT created a considerable time delay to surgical intervention. Employing TEG® to identify adequate fibrin polymerization permitted the insertion of the SEPS® drain in this patient. The role of TEG® requires additional validation in regards to its sensitivity and clinical applicability, but if the assay is readily available within an institution, it may be a valuable tool to investigate hemostasis and effectiveness of controversial reversal strategies in patients on dabigatran requiring emergent procedures.

Conflict of interest The authors declare that they have no conflict of interest.

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