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Fatal Intracerebral Hemorrhage Associated with Administration of Recombinant Tissue Plasminogen Activator in a Stroke Patient on Treatment with Dabigatran

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Dabigatran is an oral anticoagulant that has been recently approved in Europe for prevention of stroke in patients with non-valvular atrial fibrillation (NVAF), demonstrated to be equally safe or safer or at least as effective as warfarin [1].

In selected patients, we have the opportunity of thrombolysis treatment within 4.5 h after onset of ischemic stroke (IS) [2, 3] in order to minimize the risk of bleeding complications. Concomitant use of anticoagulants is a contraindication for administration of recombinant tissue plasminogen activator (rtPA) even if the international normalized ratio is <1.7 [4]. There is little information on bleeding risk in patients treated with rtPA while taking dabigatran [5, 6].

We report a 62-year-old diabetic man who underwent electric cardioversion for NVAF detected 2 months previously, who refused to take acenocoumarol and who was pretreated only with enoxaparin for 1 month. After the procedure, he was treated with dabigatran 110 mg twice daily, as an off-label situation. Three hours after taking the third dose, he had an abrupt onset of aphasia and right hemiplegia. The National Institutes of Health Stroke Scale score was 18. A non-contrast head computed tomography (CT) scan was normal. Perfusion CT revealed a deficit of $>2/3$ of the left middle cerebral artery area (fig. 1a). His blood pressure was 142/78 mm Hg and his glycemic level was 233 mg/dl. Coagulation parameters were: platelet count $154 \times 10^9/l$ (normal range 150–450), prothrombin time 14.6 s (normal range 8–14), international normalized ratio 1.29 (normal range 0.7–1.5), activated partial thromboplastin time 37.1 s (normal range 24–38) and fibrinogen level 293 mg/dl (normal range 200–450).

After obtaining informed consent, thrombolysis was initiated at 190 min from stroke onset. The neurological status did not change. Twelve hours later, the patient became drowsy and fell into a coma shortly thereafter. A CT brain scan showed a lobar hemorrhage with mass effect (fig. 1b). Control coagulation parameters were normal. The patient was intubated and transferred to an intensive care unit where he died 2 days later.

To the best of our knowledge, this is the first report to describe a fatal bleeding complication in a patient treated with dabigatran who had an IS and was treated with intravenous rtPA.

Fig. 1. **a** Perfusion CT of the brain. **b** CT scan 12 h after rtPA perfusion.

Table 1. Main clinical characteristics of patients reported

Study	Age years/sex	Dabigatran dose, mg	Last dose h	PT, s	aPTT, s	INR	NIHSS	rtPA time onset, min	Outcome
De Smedt et al. [5]	46/F	NA	7	NA	34.8	1.2	19	just below 270	improvement (12)
Matute et al. [6]	76/F	220 o.i.d.	15	11.4	30.6	1	4	120	asymptomatic (0)
Present study	62/M	110 b.i.d.	3	14.6	37.1	1.29	18	190	death

Figures in parentheses are National Institutes of Health Stroke Scale scores.

PT = Prothrombin time; aPTT = activated partial thromboplastin time; INR = international normalized ratio; NA = not available; o.i.d. = one per day; b.i.d. = twice daily.

After regulatory approval, more patients with NVAf will be treated with dabigatran and some of them will develop an IS, forcing the clinician to decide whether to treat these cases with rtPA or not, or use a lower dose of the drug [7]. Including ours, only 3 diverse cases have been reported so that it is difficult to draw any conclusions (table 1). It is possible that a shorter time interval between the last dabigatran dose and rtPA administration may be a critical factor in the increased risk of bleeding, considering the pharmacological characteristics of the drug.

Secondary intracerebral hemorrhage might have occurred even without rtPA or dabigatran use, due to large perfusion deficit or diabetes [8].

Our case warrants caution when deciding on the administration of rtPA in patients treated with dabigatran who have an IS.

Disclosure Statement

The authors state that there are no conflicts of interest.

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