Proposed Approach to Thrombolysis in Dabigatran-Treated Patients Presenting with Ischemic Stroke

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Background: Acute ischemic stroke thrombolysis in patients taking dabigatran is controversial because of a presumed increased risk of symptomatic hemorrhagic transformation. Using data from our local hematopathology laboratory, we developed a thrombolysis protocol for acute ischemic stroke patients taking dabigatran. *Methods:* A local thrombin time (TT)–dabigatran concentration relationship was calculated using dabigatran calibrators. The effect of dabigatran on activated partial thromboplastin time (aPTT) and prothrombin time (PT) (international normalized ratio [INR]) was also measured. A protocol was developed, in which a dabigatran concentration less than 10 ng/mL (corresponding to a TT $<$ 38 seconds or a normal aPTT) was selected as the upper limit for thrombolysis. Consecutive patients presenting with acute stroke were then enrolled in this prospective study. *Results:* In the 8 months after development of the protocol, 13 potential thrombolysis candidates taking dabigatran were assessed at a median (interquartile range) time of 192 (143) minutes. The median National Institutes of Health Stroke Scale score was 18 (20). The mean time from arrival to TT, aPTT, and PT (INR) results were 39 $\pm$ 4.1 minutes, 21 $\pm$ 6.5 minutes, and 21 $\pm$ 6.5 minutes, respectively. Based on TT/aPTT, 4 patients were ineligible for thrombolysis. Six patients were not treated because of minor or resolving symptoms and another presented with intracerebral hemorrhage. Two patients were treated with intravenous tissue plasminogen activator (tPA), without symptomatic hemorrhagic transformation in either case. In 3 patients (42.8%), aPTT was normal, despite a prolonged TT. *Conclusions:* Administration of intravenous tPA in dabigatran-treated patients is feasible. Although, the relationship between dabigatran concentrations and coagulation measures varies between laboratories, individual protocols, preferably based on TT, can be developed at acute stroke treatment centers. **Key Words:** Thrombolysis—anticoagulation—stroke—dabigatran—thrombin time—partial thromboplastin time.

Introduction

The use of dabigatran for stroke prevention in patients with atrial fibrillation has increased significantly since its approval in 2010.[1] Although clinicians are concerned about dabigatran-related bleeding complications, ischemic stroke presents a significant management challenge because of the absence of tests to measure dabigatran plasma concentrations in a timely manner in most centers.

The risk of hemorrhagic transformation after thrombolysis in dabigatran-treated patients is unknown, but presumed to be higher, based on experience with warfarin.[2]

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In warfarin-treated patients, thrombolysis selection is based on international normalized ratios (INRs),[3] which are unhelpful in cases of dabigatran treatment. Suggested tests of dabigatran anticoagulant activity include activated partial thromboplastin time (aPTT) and thrombin time (TT).[4] At this point, no safe aPTT or TT values have been established for thrombolysis. We hypothesized that aPTT and/or TT can be used to select appropriate patients for stroke thrombolysis and developed a protocol for tissue plasminogen activator (tPA) administration in this setting.

Methods

Dabigatran Concentration Assessment Tests

A TT (human source serum thrombotic accelerator (STA) thrombin reagent; Diagnostica Stago, Asnières Sur Seine, France) dabigatran concentration curve (Fig 1) was generated using dabigatran calibrators (courtesy Joachim Stangier, Boehringer Ingelheim Pharma GmbH & Co, KG, Biberach an der Riss, Germany). TT was also measured in patient samples with both normal (n = 8) and elevated fibrinogen levels (n = 4). Elevated fibrinogen levels results in a spuriously low or prolonged TT.[5]

aPTTs were measured at each dabigatran concentration using SynthASil reagent (HemosIL; Instrumentation Laboratory Company, Bedford, MA) and both the STA-R coagulation analyzer (Diagnostica Stago) and STA-comp (Compact) coagulation analyzers (Diagnostica Stago).

Thrombolysis Patient Selection Algorithm

An algorithm for selection of tPA candidates was then developed based on TT and aPTT thresholds (Fig 2). Treatment decisions were all made as part of routine stroke care. This was not a research protocol and was, therefore, not submitted to our local Internal Review Board. Similarly, patients were not asked to sign consent as intravenous tPA is standard of care in our centers. The unique situation was discussed with the patients and family when the patients arrived to emergency department. In patients who were aphasic or had decreased consciousness and had no family member available for discussion, the attending physician made the treatment decision and the family/patient were informed later. TT and fibrinogen levels were obtained in patients with a history of dabigatran use. Patients with a TT of less than 38 seconds, corresponding to dabigatran concentrations less than 10 ng/mL, were considered potential tPA candidates. It was not possible to obtain TT at telestroke centers. Thrombolysis decisions were made using aPTT values alone at these sites. As the relationship between aPTT prolongation and dabigatran concentrations is not linear,[4] only patients with normal aPTT values were considered eligible for tPA.

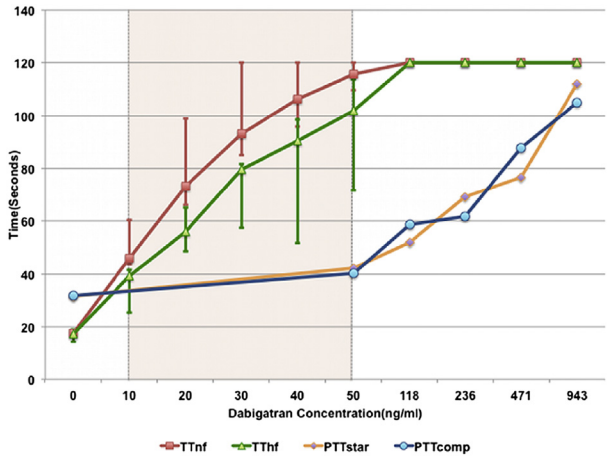

Figure 1. *Dabigatran concentration–thrombin time and activated thromboplastin time plot. Abbreviations: TTnf, thrombin time (normal fibrinogen); TThf, thrombin time (high fibrinogen); aPTTstar, activated plasma thromboplastin time (STA-R coagulometer); PTTcomp, activated plasma thromboplastin time (compact coagulometer).*

All patients underwent noncontrast computed tomography (CT). CT angiography (CTA) of the neck and head arteries and CT perfusion of the brain were performed when possible. The CTA is standard at our tertiary care sites but is not always completed as part of telestroke assessments. The noncontrast CT was evaluated for early signs of ischemia, and if more than one third of the symptomatic vascular territory was involved, then the patient was not considered eligible for intravenous thrombolysis. The treatment algorithm was circulated to attending stroke specialists and fellows. We prospectively collected data from all patients with a history of dabigatran use who presented with acute ischemic stroke.

Results

In the 8 months after protocol development, 13 (6 women) potential thrombolysis candidates taking dabigatran with a mean (SD) age of 70.4 ± 12.6 years were assessed with CT scan at a median (interquartile range) time of 192 (143) minutes (Table 1). Symptoms resolved to the point of nondebilitating deficits by the time of baseline CT scan in 6 patients. None of these patients had a major arterial occlusion visible on CTA. Three patients presented with a partial anterior circulation syndrome, 1 with a lacunar syndrome, and 2 had posterior circulation syndromes.

One patient had dabigatran-associated intracerebral hemorrhage (TT > 120 seconds). The 6 remaining patients had a median (interquartile range) National Institutes of Health Stroke Scale score of 18 (20). The mean time from arrival to TT, aPTT, and prothrombin time (INR) results were 39 ± 4.1 minutes, 21 ± 6.5 minutes, and 21 ± 6.5 minutes, respectively. Based on TT/aPTT, 4 patients were ineligible for thrombolysis (dabigatran concentrations > 10 ng/mL).