Dabigatran Plasma Levels in Acute Cerebrovascular Events

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Background: Oral anticoagulation with dabigatran was shown to be effective for stroke prevention in patients with nonvalvular atrial fibrillation without the need for laboratory monitoring. However, a recent publication based on data of the Randomized Evaluation of Long-Term Anticoagulation Therapy study reported that ischemic stroke and bleeding outcomes are correlated with dabigatran plasma concentration (DPC). DPC was determined at a prespecified time point and correlated with cardiovascular events at any time during follow-up. Because of the known variability of DPC, among others depending on renal function, this approach might compromise data evaluation. We report on dabigatran plasma levels in acute cerebrovascular events. *Methods:* Consecutive patients with acute ischemic stroke (AIS) or intracerebral hemorrhage (ICH) while taking dabigatran were retrospectively identified if admission DPC was available. DPC was determined using the diluted thrombin time (Hemoclot (HYPHEN BioMed, Neuville sur Oise, France)). Creatinine clearance (CrCl) was determined by measuring creatinine in plasma and 24-hour urine. *Results:* Fifteen AIS and 4 ICH patients were included. Median DPC on admission was significantly higher in ICH patients than in AIS patients (135 ng/mL [interquartile range {IQR} 79-218] and 69.1 ng/mL [IQR 20.6-85.0], respectively; $P = .035$). Increased CrCl (values above published normal range) was correlated with lower median DPC (60 ng/mL [IQR 10-69] versus 100 ng/mL [IQR 79-157] in patients with normal CrCl, $P = .01$). *Conclusions:* Higher DPC was found in ICH patients than in AIS patients in temporal proximity to the event. Both decreased and increased renal functions seem to have an important influence on DPC. **Key Words:** Dabigatran—anticoagulant—ischemic stroke—intracerebral hemorrhage—pharmacokinetics—renal function.

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Introduction

Stroke is one of the leading causes of morbidity and mortality worldwide.[1] Among others, atrial fibrillation is one of the major risk factors for stroke.[2] Regarding stroke prevention in patients with nonvalvular atrial fibrillation, dabigatran has been shown to be superior to warfarin in the higher dose (150 mg twice daily [bid]) and noninferior in the lower dose (110 mg bid) at a significantly decreased rate of intracranial bleedings. This could be proven for a fixed dosing scheme without the need for laboratory monitoring.[3] However, a recent publication of additional Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial data reported higher dabigatran plasma concentration (DPC) levels in association with the occurrence of major bleedings. Reversely, lower levels were found in patients who suffered acute ischemic stroke (AIS) or who had no cardiovascular event during follow-up.[4] The authors concluded that ischemic stroke and bleeding outcomes are correlated with DPC.[4] However, blood samples were taken at prespecified time points without temporal correlation to the recorded cardiovascular event. Given the known large variability of DPC over time,[4,5] this missing temporal correlation might inaccurately influence the results. In the present study, we report on the first available DPC data in AIS and intracerebral hemorrhage (ICH) patients in temporal proximity to the event.

Methods

Patient Selection

Consecutive patients with AIS or ICH, known symptom onset, and available DPC on admission were retrospectively identified from a prospectively collected database. DPC on admission was performed only in those patients who reported regular dabigatran intake approved by the next of kin. Patients were included even if the trough sample criterion (blood sample collected within 10-16 hours after the previous dabigatran dose)[4] was not fulfilled. On-label use of dabigatran according to the European Medicines Agency labeling as stroke prevention in the context of atrial fibrillation was mandatory. The study was approved by our institutional review board.

Acquisition of Data

DPC, time of last intake, clinical characteristics, laboratory results, and known factors influencing DPC such as creatinine clearance (CrCl), age, sex, and CHA_2DS_2-VASc score were obtained from medical records. DPC was measured using the diluted thrombin time (Hemoclot).[6] CrCl was determined by measuring creatinine in plasma and 24-hour urine during the hospital stay. CrCl was defined as increased if the age- and sex-adjusted threshold as suggested by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative[7] was exceeded. Dose-normalized DPC was calculated by dividing DPC by the administered dose.[4]

Analysis and Statistics

Results are presented as number and percentage or median and interquartile range (IQR) as appropriate. Interval and ordinal variables between the 2 groups were compared using the Mann–Whitney *U*-test. Fisher's exact test was used for the analysis of dichotomous variables between the ICH and AIS groups. Linear regression was used for the correlation between CrCl and dose-normalized DPC. Statistical analyses were performed using the IBM SPSS Statistics 21 software package (IBM Corporation, Armonk, New York, United States). A P value less than .05 was considered statistically significant. Tests were 2-tailed.

Results

The Hemoclot test was introduced in our laboratory in October 2012. Until August 2015, DPC was determined for 15 AIS patients and 4 ICH patients with known symptom onset on hospital admission. Two AIS patients with minor strokes (both with minor newly detected deficits [National Institutes of Health Stroke Scale score of 2] lasting >24 hours without correlate in cerebral imaging) and 4 other ischemic stroke patients with reported symptom onset of more than 3 days before admission and reported regular dabigatran intake did not receive DPC on admission due to the discretion of the treating physician. In all cases, DPC on admission was not necessary for further treatment decisions. All other patients admitted to our hospital with AIS or acute ICH and reported regular dabigatran intake received DPC on admission and were included. Patient characteristics are given in Table 1. The median time between the last dabigatran intake as indicated by the patient and the next of kin and blood sampling was 10 hours (IQR 7-12) in AIS patients and 15 hours (IQR 7-21) in ICH patients (P = .19). The median DPC was 135 ng/mL (IQR 79-218, dose normalized 1.08 ng/mL/mg [IQR .64-1.98]) in ICH patients and 69.1 ng/mL (IQR 20.6-85.0, dose normalized .59 ng/mL/mg [IQR .19-.77]) in AIS patients (P = .04). CrCl was measured in 2 ICH patients who showed a normal CrCl value (43 and 56 mL/minute) and in 11 AIS patients (97 mL/minute, IQR 65-162). CrCl was classified as increased in 7 AIS patients (64%). Patients with increased CrCl values had lower DPCs than those with normal CrCl (60 ng/mL [IQR 10-69] and 100 ng/mL [IQR 79-157], respectively, P = .01; dose normalized: .6 ng/mL/mg [IQR .1-.6] and .9 ng/mL/mg [IQR .6-1.4], respectively, P = .02). Correlation between CrCl and DPC in this cohort is illustrated in Figure 1.

Discussion

For the first time, we could show that in patients receiving dabigatran as stroke prevention, higher DPC can