BRIEF OBSERVATION

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Interpretation of Point-of-care INR Results in Patients Treated with Dabigatran

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ABSTRACT

BACKGROUND: Point-of-care devices for measurement of the international normalized ratio (INR) are commonly used to monitor therapy and maintain therapeutic levels of anticoagulation in patients treated with vitamin K antagonists. Dabigatran, a new oral, reversible direct thrombin inhibitor approved for stroke prevention in patients with atrial fibrillation does not require routine coagulation monitoring. However, case reports have identified falsely elevated point-of-care INR levels in patients treated with dabigatran using one of these devices (Hemochron). This in vitro study was designed to verify this issue.

METHODS: We compared INR levels in whole blood and plasma using a Hemochron Jr. Signature+ point-of-care device (International Technidyne Corporation, Edison, NJ) with routine laboratory monitoring, using blood from healthy volunteers that was spiked with increasing concentrations of dabigatran.

RESULTS: Prothrombin time and INR levels were increased about 2- to 4-fold with the point-of-care device compared with laboratory measures across the plasma dabigatran concentration range 50-1400 ng/mL. At plasma concentrations of dabigatran likely to be observed in patients, at a dose of 150 mg twice daily (60-275 ng/mL), whole blood point-of-care INR values increased from 1.7 to 4.0, versus 1.1 to 1.5 measured with the laboratory coagulometer. Similar differences in prothrombin time were observed in plasma samples.

CONCLUSIONS: INR levels in patients taking dabigatran are substantially higher using a Hemochron Jr. point-of-care device compared with laboratory values. We discourage the use of these devices specifically, as well as the use of the INR in general, for measuring the anticoagulant effect of dabigatran.

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KEYWORDS: Coagulation assays; Dabigatran; Dabigatran etexilate; Direct thrombin inhibitor

Dabigatran etexilate is an oral direct thrombin inhibitor approved in several countries for the prevention of thromboembolism in atrial fibrillation.[1-3] Dabigatran has a predictable pharmacokinetic profile, allowing for a fixed-dose regimen without the need for routine coagulation monitoring. However, in some situations such as suspected overdose, the perioperative setting, or patients with active bleeding, measurement of anticoagulant activity may be indicated.

According to the product label, assessment of the activated partial thromboplastin time is the preferred method for detection of excess anticoagulant efficacy with dabigatran.[1-3] Quantitative tests, specifically the ecarin clotting time and Hemoclot Thrombin Inhibitor assay (Hyphen BioMed, Neuville-sur-Oise, France), a sensitive diluted thrombin time assay, provide more precise information, and may be particularly useful in urgent clinical situations such as active bleeding or when an invasive procedure is indicated. Both the prothrombin time and the international normalized ratio (INR) tests are insensitive measures and should not be used for evaluating the anticoagulant effect of dabigatran.[4] Despite this recommendation, patients transitioning between warfarin and dabigatran may inadvertently have a point-of-care INR measurement. Recent reports have raised questions about the accuracy of point-of-care measurements in dabigatran-treated patients, as falsely elevated levels were noted when compared with labo-

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ratory INR testing.[5,6] This in vitro study aimed to investigate this issue by comparing INR measurement using a point-of-care device with routine laboratory testing in healthy volunteers.

METHODS

The study was approved by a Local Research Ethics Committee, and all 4 subjects (2 male and 2 female) gave written informed consent. Venous blood samples (20 mL in total) were collected from each volunteer into 3.2% sodium citrate tubes, separated into aliquots, spiked with increasing concentrations (50-1400 ng/mL) of dabigatran (Boehringer Ingelheim, Ingelheim, Germany), and incubated at 37°C for at least 5 minutes. Whole blood samples (100 μL) were applied to individual disposable prothrombin time cuvettes, which were inserted into the Hemochron Jr. Signature+ point-of-care device (International Technidyne Corporation, Edison, NJ). Single-test cartridges were used and operated according to the manufacturer's instructions. In the device, blood was mixed with rabbit brain-derived thromboplastin (international sensitivity index ~1.0). The Hemochron device relies on the optical detection of mechanical clot properties to calculate the INR and estimate the prothrombin time in plasma.

Duplicate whole blood aliquots were used for laboratory prothrombin time determination by the CL4 coagulation analyzer (Behnk Elektronik GmbH & Co. KG, Norderstedt, Germany) and Thromborel S recombinant thromboplastin (Siemens Healthcare Diagnostics, Marburg, Germany). Local calibration of the international sensitivity index gave an identical value to that provided by the manufacturer for this reagent/analyzer combination (international sensitivity index = 1.07), and calculated INR values were obtained from the measured prothrombin time values. All appropriate standards referred to in the manufacturers' instructions were used for calibration of the results. Plasma samples were obtained by centrifugation (10,000 rpm, 5 minutes; 4°C) of the remaining citrated whole blood samples containing dabigatran, and activated partial thromboplastin time levels (PTT Reagent, Diagnostica Stago, Asnières, France) were calculated for comparison. Data were summarized as arithmetic mean ± SE.

CLINICAL SIGNIFICANCE

- Although coagulation monitoring is not routinely indicated with dabigatran, it may be advisable in some situations to identify patients at increased bleeding risk.
- Point-of-care devices should not be used for measurement of international normalized ratio in patients taking dabigatran, as levels are falsely elevated.
- Laboratory-activated partial thromboplastin time measurement is preferred to detect excess anticoagulant activity, with quantitation using either the Hemoclot Thrombin Inhibitor assay or ecarin clotting time.

RESULTS

Across the dabigatran concentration range tested, INR levels were consistently higher (by 2- to 4-fold) when measured using the Hemochron Jr. point-of-care device compared with the laboratory-based coagulometer (**Figure 1**). At representative plasma concentrations of dabigatran, likely to be observed in patients, at a dose of 150 mg twice daily (60-275 ng/mL),[3] whole blood point-of-care INR values increased from 1.7 to 4.0, compared with 1.1 to 1.5 when measured with the laboratory coagulometer (**Table**). It is notable that at dabiga-

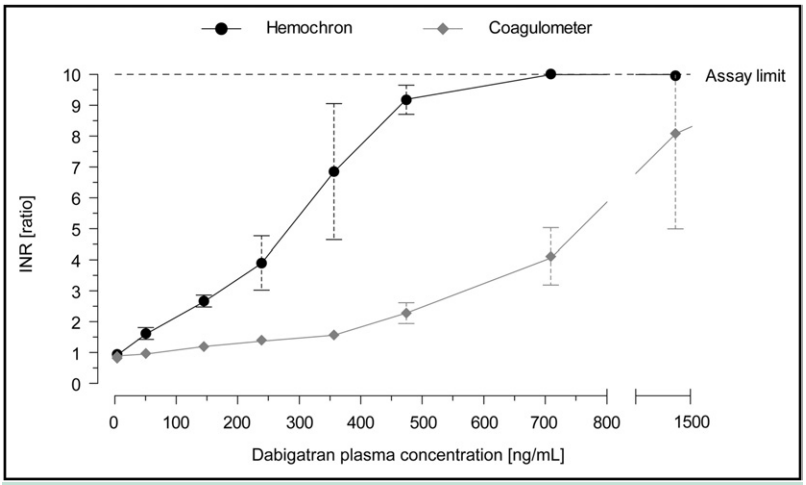

Figure 1 Effect of dabigatran on citrated whole blood international normalized ratio (INR) measurement using a laboratory coagulometer and Hemochron Jr. (International Technidyne Corporation, Edison, NJ) point-of-care system. In vitro results from 4 healthy volunteers. Arithmetic mean and SE are shown.