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Therapeutic Drug Monitoring
Issue

Identification of Different Patterns of Dabigatran In Vivo Bioactivation in Patients on Maintenance Anticoagulation Therapy

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To the Editor:

Dabigatran is a direct thrombin inhibitor characterized by a wide therapeutic window, faster onset and offset of action, and no need for routine blood monitoring.[1] Nonetheless, growing evidence is now available showing that interindividual variability exists in the pharmacokinetics of dabigatran, being significantly altered by renal dysfunction, patient's age, or comedications.[1,2] The presence of these conditions, if not adequately taken into account, would eventually lead to suboptimal or excessive anticoagulation, with possible therapeutic failure or development of adverse drug reactions, including major bleeding.[3]

Dabigatran is administered as etexilate, a prodrug that is rapidly absorbed and quantitatively converted into 2 intermediate prodrugs, namely desethyl dabigatran etexilate and dabigatran ethyl-ester (pharmacologically active), which are subsequently transformed into dabigatran (Fig. 1).[4] Alterations in the bioactivation pathway could add further variability to both drug pharmacokinetics and, eventually, the response to dabigatran therapy. We have thus investigated the mechanism of bioconversion of dabigatran etexilate to dabigatran in vivo in patients on maintenance anticoagulation therapy. formatGraphic.tt2 begin

Figure 1

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A high-performance liquid chromatography coupled with tandem mass spectrometry method was developed to measure concomitantly the plasma concentrations of dabigatran etexilate, dabigatran, desethyl dabigatran etexilate, and dabigatran ethyl-ester based on a recently published assay for dabigatran quantification.5 High-purity powder for the preparation of the calibrators of dabigatran etexilate was kindly donated by Boeringher Ingelheim (Milan, Italy), whereas other compounds were purchased from TRC (Toronto, Canada). Briefly, plasma samples were purified by solid phase extraction using C18 Bond Elute cartridges. All analytes were quantified by a multiple-reaction monitoring mode with the transitions m/z 628.3 > 289.2 for dabigatran etexilate, 472.1 > 289.2 and 472.1 > 172.0 (confirmation transition) for dabigatran, 603 > 289.2 for desethyl dabigatran etexilate, and 500.3 > 289.2 for dabigatran ethyl-ester. The described method was validated according to the European Medicines Agency Guidelines for bioanalytical method validation.6 For all analytes, the intra- and inter-day inaccuracy and imprecision were in every instance <13.4%. For all analytes, the lower limit of quantification was set at 1.0 ng/mL (imprecision <=20%). The method was subsequently applied for the assessment of plasma trough concentrations of dabigatran etexilate, dabigatran, and the 2 intermediate prodrugs in 40 patients on maintenance dabigatran etexilate during routine outpatient visits (visits 1, 2, and 3 respectively at 3, 6, and 12 months after starting anticoagulation therapy).

A wide interindividual variability of dabigatran plasma trough concentrations was observed during the 3 visits (coefficient of variations 86%, 64%, and 62% at visits 1, 2, and 3, respectively), with measured drug levels (and variability) in the expected range according to the available literature.7,8 Interestingly, the prodrug dabigatran etexilate was detected in some patients during each visit (Table 1), with concentrations ranging from 1 to 15 ng/mL. Similarly, quantifiable concentrations of the prodrug intermediates desethyl dabigatran etexilate and dabigatran ethyl-ester were found overall in 32% and 8% of patients. The presence of these intermediates was not linked to the dabigatran dose administered or to single patients. Conversely, we found that, when the etexilate prodrug was present, the intermediate metabolites were also detected. formatGraphic.tt2 begin Table

Table 1

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As the first finding of this investigation, we confirmed that, despite median dabigatran concentrations comparable with values measured in the registrative trials, this drug was associated with wide pharmacokinetic interindividual variability, in agreement with recent data from real-life settings.7,8 Moreover, the characterization of the pharmacokinetics of dabigatran in patients on oral anticoagulation therapy we performed reveals the existence of different patterns of drug bioactivation, eventually leading to incomplete dabigatran conversion in selected cases. Previous studies in healthy volunteers given single dose of dabigatran etexilate have shown that this prodrug is rapidly and completely

converted to dabigatran.9,10 Accordingly, one could expect that dabigatran etexilate cannot be found in patients on maintenance anticoagulant therapy. Conversely, we observed that 9%–20% of our patients have prodrug concentrations above the lower limit of quantification of the method. To better evaluate the bioactivation step, we also looked at the 2 main intermediate prodrugs, namely desethyl dabigatran etexilate and dabigatran ethyl-ester. Again, according to the available literature from healthy male volunteers,4 these intermediates are expected to be present, if any, only in trace amounts, given their very rapid conversion to dabigatran. According to our data, this may be eventually the case for dabigatran ethyl-ester, which was measured only in a minority of patients (from 7% to 12%), but not for desethyl dabigatran etexilate, which was found in 20%–40% of our patients. Taken together, these findings suggest that incomplete bioconversion to dabigatran may take place in selected patients. This may be possibly related to inadequate activity of carboxyl esterases (CES1, CES2), the class of enzyme involved in the conversion from dabigatran etexilate to dabigatran. Indeed, it has been recently shown that the catalytic activity of CES1 and CES2 can be significantly affected by several factors, such as sex (women have higher CES1 activity), age (the activity increases from birth to adulthood), drug interactions, hepatic diseases (impaired activity),11 and also by individual genetic background.12

The main limitation of our investigation is represented by the lack of clinical information on patients' characteristics (ie, creatinine levels and liver enzymes), as well as data on response to therapy (ie, bleeding versus treatment failure). The assessment of the potential associations between dabigatran concentrations and clinical outcome is beyond the scope of this study. Here, we would like just to give a picture of the bioconversion pathway of dabigatran in a real-life scenario.

In conclusion, different patterns of dabigatran in vivo bioactivation have been identified in patients on maintenance anticoagulation therapy. Although the clinical impact of these findings warrants future investigations, they might argue against a fixed-dose approach for dabigatran, eventually asking for individualized dose regimens.

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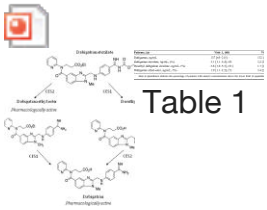
Table 1

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