Letter to the Editors

Is the dose of dabigatran really more predictable than warfarin?

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We read with interest a recent commentary on the dosing of dabigatran 'Optimizing the dose of dabigatran etexilate' [1]. The author argues that warfarin fails to meet the required target profile for an oral anticoagulant because of large inter- and intra-individual variability in dosage requirements [1]. He notes that this variability can be attributed to the influence of patient characteristics, such as age, body weight, genetic polymorphisms, diet, organ dysfunction and drug interactions, on warfarin pharmacokinetics. By contrast, the author contends that dabigatran pharmacokinetics exhibit low to moderate variability overall and that differences between patients in terms of measured $C_{\max}$ and AUC can largely be explained by differences in renal function [1]. We interpret the message to be that dabigatran is a step towards the required target profile for an oral anticoagulant and would be expected to have a 'readily predictable dosage'. However, we wonder whether dabigatran will ultimately prove to be all that different from warfarin in terms of the need to individualize dosage and to monitor anticoagulation.

The suggestion that dabigatran has less variable pharmacokinetics than warfarin cannot be substantiated with evidence from published population analyses. The unexplained variability in dabigatran clearance (CL) has been found to be approximately 50% (CV) [2], a value that reflects the variability remaining after differences in renal function between patients had been taken into account. By contrast, the unexplained variability in S-warfarin CL after accounting for important covariates (e.g. CYP2C9 genotype) has been reported to be 30–40% (CV) [3, 4]. Indeed a level of variability of the order of 30–60% (CV) has been shown to be typical for the CL of all the new anticoagulants [5]. In addition, dabigatran etexilate (the prodrug) is poorly soluble at pH > 3.0 and is a substrate for the efflux transporter P-glycoprotein (P-gp) in the gut wall resulting in a low fraction absorbed (6–7%) [6]. Pharmacokinetic interactions between dabigatran and proton pump inhibitors and P-gp inhibitors or inducers would be expected to provide additional sources of pharmacokinetic variability. Consequently, the factors that make war-

farin a less than ideal oral anticoagulant may also apply to dabigatran, e.g. drug interactions, organ dysfunction, genetic polymorphisms (e.g. P-gp), age and body size. In short, according to available evidence the pharmacokinetics of dabigatran are not less variable than warfarin and hence are not more predictable.

In addition, we question whether it is mechanistically possible to produce a drug that will fulfil the requirements of an ideal anticoagulant. There will always be a fine line between therapeutic anticoagulation and the risk of bleeding, regardless of the anticoagulant. This is due to the innate variability and sensitivity of the coagulation network which means that small perturbations in the network can result in significant influences on the overall effect. We contend that any drug that perturbs this system will inevitably have a narrow therapeutic range and will be likely to require monitoring of anticoagulation to ensure safe and effective prescribing [7]. Furthermore, we speculate that there may be less natural dampening of the coagulation system with anticoagulants that act close to the final stage of clot formation (i.e. an anticoagulant that inactivates thrombin) which means variability in drug concentration may well result in more profound variability in coagulation response.

In summary, all oral anticoagulants seem to have similar pharmacokinetic variability and will be subject to a narrow therapeutic range. We suggest that new anticoagulants, such as dabigatran, will require monitoring of anticoagulation to determine the dose that best meets the needs of each patient.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the

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