Dabigatran: rational dose individualisation and monitoring guidance is needed

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Abstract

Dabigatran is the first oral anticoagulant to be introduced in New Zealand without prescribing restrictions for over 50 years. Not surprisingly, the drug has created a great deal of interest amongst health care providers as well as the general public and media. There seems to be a general feeling that warfarin, with its requisite dose adjustments and INR monitoring, is an outdated drug and should be shelved in favour of this novel agent. The assumption is that the newer drug must be better and safer as well as easier to use. Much of the literature associated with dabigatran encourages this view, stressing that dabigatran is a ‘game changer’ with the advantage of fixed dosing for most patients and no anticoagulation monitoring. In this paper we question whether dabigatran can really live up to these expectations. We suggest that the safe and effective prescribing of dabigatran, like all anticoagulants used in therapeutic doses, will most likely require dose individualisation and selective monitoring. This requirement should not be viewed as a failure for dabigatran but rather as a success for rational therapeutics.

Dabigatran is an orally-active direct thrombin inhibitor currently licensed for use in non-valvular atrial fibrillation and for the prevention of venous thromboembolism following joint replacement surgery. It is marketed in New Zealand under the brand name Pradaxa® and was listed in the Pharmaceutical Schedule without Special Authority in July 2011. Whilst we believe that the availability of this drug will provide more flexibility for the prescriber, and may lead to improved outcomes for some patients, we have major concerns about the lack of rational advice on dosing and monitoring, particularly for patients at high risk of bleeding.

Current dosing guidance for dabigatran

The current dosing advice for prescribers is puzzling. The New Zealand datasheet states that all patients get a fixed dose unless (1) they have atrial fibrillation and are over 80 years old, or, (2) if they have had orthopaedic surgery and have impaired renal function.¹ No comment is made as to why the suggested dose reductions for age and renal impairment do not apply equally to both indications. This guidance seems to fly in the face of reason.

Drugs that are cleared renally, such as dabigatran, are reliant on glomerular filtration rate (GFR) for elimination. A normal GFR may be in the order of about 100 mL/min. If the patient has a GFR of half or one-third normal (e.g. 30–50 mL/min) the clearance of the drug will also be reduced and plasma concentrations will increase proportionately. A dose reduction is therefore required to normalise drug exposure and reduce the risk of adverse effects.
There is a paucity of independent prescribing guidance for dabigatran. The recent bulletin from the Best Practice Advocacy Centre (BPAC) is a welcome and thorough overview of dabigatran for primary care practitioners but falls short when it comes to specific advice about dosing. Rather, BPAC advocates that prescribers take a ‘cautious approach’, particularly when prescribing for patients at high risk of bleeds such as those with renal impairment. This leaves the practitioner with little practical guidance with which to meet the needs of individual patients.

Consider, for example, the hypothetical case of a 79-year-old female with atrial fibrillation who has a lean mass of 50 kg and a normal serum creatinine of 110 µmol/L. Her estimated creatinine clearance calculated by the Cockcroft and Gault formula would be 33 mL/min. This patient would clearly be at risk of increased drug exposure and bleeding if a fixed dose were given, a situation that would no doubt be recognised by a cautious prescriber. However, the fact remains that the dosing guidance in this situation is lacking and contradictory.

In the absence of a validated means of monitoring the effectiveness and safety of therapy the physician is left guessing as to the best course of action. If the patient had been post-orthopaedic surgery, then the dose would be reduced according to the recommendations in the datasheet without question. However since the patient has atrial fibrillation the manufacturer’s guidance suggests that it is perfectly reasonable to continue the dose at 150 mg twice daily without adjustment.

The need for dose individualisation

As with any anticoagulant, the use of dabigatran carries a risk of bleeding. Major bleeding is an independent predictor of death and is associated with increased cost and longer duration of hospital stay. Arguably, there is a fine line between the magnitude of anticoagulation required to prevent clots in susceptible patients and that which is sufficient to cause bleeding, especially in a patient population where a variety of vascular disorders are common. This is independent of the drug itself but relates to the innate complexity and sensitivity of the coagulation network, which is the target for anticoagulant action.

In short, we suggest that all anticoagulants used in therapeutic doses will have a narrow therapeutic range and will require selective monitoring to ensure optimal effectiveness and the prevention of side effects. In addition, analysis of the coagulation system (based on Wajima et al) suggests that there may be less natural dampening of the coagulation system with anticoagulants that target the later stages of coagulation. Hence, the anticoagulant effects of drugs like dabigatran that act close to the final stage of clot formation will, in theory, be more sensitive to the prescribed dosing regimen and to inherent variability in the dose-concentration relationship (pharmacokinetics).

When dabigatran was introduced into the New Zealand market the media release from Pharmac claimed “... [dabigatran] is literally a game-changer and demonstrates PHARMAC’s desire to move relatively swiftly to fund genuinely innovative medicines”. Although the spirit of the statement is appropriate, the suggestion that introducing a new drug is all that it takes to change the game is misleading.
Individualisation of existing medicines has often been shown to be quantitatively more important than the introduction of a new medicine. For instance, an individualised regimen of enoxaparin treatment, based on renal function and body composition, resulted in a number needed to treat (NNT) of 8 patients to reduce bleeding events when compared to conventional weight-adjusted dosing. This is a very favourable number when compared to many new interventions. For example, simvastatin was found to have an NNT for one year of 167 for preventing all cardiovascular events in the Scandinavian Simvastatin Survival Study (4S). We therefore contend that the act of introducing a new anticoagulant will not necessarily change the game without knowledge of how best to individualise its use.

So why would dabigatran be considered a games changer? Perhaps this is because it is seen as a replacement for warfarin, with its requisite INR monitoring and dose adjustments? If so, we query whether dabigatran will ultimately prove to be all that different from warfarin and whether dose individualisation and selected anticoagulation monitoring will eventually prove important for safe prescribing. If so, the monitoring required will need to be targeted to clinical situations that are more likely to be associated with bleeding or clotting.

Is dabigatran a better choice than warfarin?

Warfarin acts by inhibiting the formation of vitamin K dependant clotting factors (II, VII, IX and X). Daily dose requirements are highly variable between patients, ranging from < 1 mg/day to > 10 mg/day. This large variability is often interpreted as a leading problem with warfarin therapy. However it also indicates that doses are being successfully adjusted to meet the needs of individual patients.

Herein lies the dichotomy between the desire for simplicity—one dose fits all, and the needs of our patients, where doses should be optimised to meet their specific requirements. Indeed from a standpoint of optimising care the warfarin dosing model is an excellent example of success. It is apparent that services that are set up for this purpose (individualising warfarin dosing) achieve better health outcomes for patients.

A related problem with warfarin is that its metabolic clearance has been found to vary between individuals due to genetic polymorphisms in cytochrome P450 enzymes (largely CYP2C9). It also interacts with vitamin K in the diet and vitamin K stores in the body resulting in variability in response. However we can measure a patient’s response to warfarin with the INR, an inexpensive test that can now be performed in the clinic or at home using a portable device.

INR results capture information about the patient’s individual response to warfarin and allow for rational dose adjustments. We could also measure a patient’s genotype to help predict a starting dose for warfarin, although this is not routinely performed in New Zealand and will only identify variability that arises from genetic differences between individuals.

Another issue is that warfarin may cause excessive bleeding after dosing that is higher than required and occasionally at the intended dose. This can be reversed by either withholding the drug or, if required promptly, administering vitamin K, and the addition of Prothrombinex-VF if urgent correction is required.
Unlike warfarin, it is claimed that dabigatran has a predictable pharmacokinetic and pharmacodynamic profile which allows for the use of fixed doses. Yet, the variability in dabigatran clearance, the pharmacokinetic parameter most important for determining the maintenance dose, has been reported to be in the order of 50% (coefficient of variation across the population) which is similar to the variability observed for warfarin clearance of 30–50%. On this basis alone dabigatran exposure is not more predictable than warfarin. Indeed it might therefore be argued that if one dose does not fit all for warfarin then why would we expect this to be the case with dabigatran? As there is a correlation between dabigatran blood concentrations and efficacy and safety outcomes, unpredicted high or low blood concentrations could increase the risk of adverse events.

There is published evidence to indicate that dabigatran exposure differs predictably between individuals. The manufacturer reports that drug exposure was 1.5–6.3-fold higher in those with renal impairment compared to healthy subjects. Exposure to dabigatran may also be altered in patients with low body weight. The Pradaxa® datasheet states that drug exposure was about 40–50% higher in female patients in primary VTE prevention studies. In atrial fibrillation patients, females had an average 30% higher trough post-dose concentration than male patients. We believe that these sex differences may relate to differences in body composition (e.g. lean body weight) between males and females. Therefore, dabigatran exposure in individuals at the extremes of body weight needs to be defined and evaluated.

Dabigatran is poorly absorbed orally because it is a substrate for P-glycoprotein, an efflux transporter responsible for limiting systemic xenobiotic exposure by pumping drug back into the gut. There are currently over 100 known polymorphic variants of the gene that codes for P-glycoprotein (ABCB1) and it is not clear what impact different genotypes will have on efflux function in many cases. By contrast, the impact of altered hepatic enzyme activity on warfarin exposure is well understood and can be measured by determining the patients genotype. In addition, several drugs and drug classes have been found to inhibit P-glycoprotein such as amiodarone, atorvastatin, felodipine, verapamil, macrolides, some antifungals as well as foods such as with grapefruit and other citrus juices. Ingestion of these drugs and foods may result in elevated plasma dabigatran concentrations and an increased risk of bleeding.

**Monitoring dabigatran therapy**

Dabigatran shows varied effects on individual coagulation screening tests. There is limited sensitivity of the PT/INR, better sensitivity, though non-linearity at lower concentrations, of the aPTT, and marked sensitivity of the thrombin clotting time (TT). The Ecarin clotting time appears to be a slightly more sensitive test but availability is currently limited in New Zealand. Data suggests that three factors affect the test results: drug concentration, the patient’s intrinsic coagulation kinetics and the variability of the screening test(s). This situation is similar to variation in the INR testing of warfarin effect, despite strenuous international efforts to standardise the test results. Further research to validate a clotting time test for monitoring dabigatran effect is required. Research is also needed to establish guidelines for monitoring.
In the absence of a validated anticoagulation measure for dabigatran, the best widely available clotting time test for monitoring and dose individualisation is probably the aPTT. Published data indicate that prolongation of the aPTT at peak drug concentration (i.e. 2–4 hours post dose) will be around 1.9x, ranging from 1.6x–2.2x or 46–65s where the reference range is 24–34s (note that values will differ where the reference range differs). This may be useful in assessing peak dose effects to confirm the dose selected, particularly in low weight patients and in those whom P-glycoprotein function is known or suspected to be abnormal. Trough aPTT values (i.e. just before the next dose) may be useful for detecting significant drug accumulation in a renally impaired patient and where low body weight or metabolic factors lead to higher values. Trough aPTT values appear to be in the range 34–45s (reference range 24–34s) but this needs confirmation. The sensitivity of the aPTT for trough measurements will be poor at low dabigatran concentrations but can be detected by the thrombin clotting time (TT).

We suggest that monitoring may be appropriate in the following situations: initial dose individualisation in patients at risk of increased drug exposure and bleeding (aPTT), patients with deteriorating renal function (aPTT), and where a patient requires urgent/emergency surgery to detect the absence of residual drug (TT). Note that trough and peak monitoring will be time-dependent and when used will require patients to attend for sample collection at the required time pre- or post-dose.

If a patient receives sustained excessive dosing of dabigatran and experiences a bleed there is currently no antidote. Efforts to produce an inhibitor of dabigatran have been reported using monoclonal antibody technology but are still at an early stage of development. Other approaches to managing bleeding rely on non-specific and local measures as noted in the Pharmac guidance document for managing bleeds. Haematologist advice should be sought for reversing the effect of dabigatran for acute surgery or in the event of acute bleeding.

The fact that the monitoring of dabigatran therapy is currently not recommended should not be misinterpreted to mean that monitoring is not required. Although the published trial data for dabigatran indicates similar or lower bleeding rates in the selected trial participants compared with warfarin, this is not enough to claim that monitoring is not required. It is well established in medical ethics that where it is possible to reduce the risk of bleeding or thrombosis as a result of inappropriate dosing, by taking reasonable actions, these actions should be taken.

Conclusions

We believe there is a clear need for rational dose individualisation and monitoring guidance with dabigatran, particularly for patients at higher risk of bleeding. This would include the elderly, those at the extremes of body weight or with renal impairment and/or on drugs with potential interactions. Patients with moderate renal impairment should receive a smaller daily dose and, based on our current knowledge, the drug should be avoided in those with severe renal impairment (calculated Cockroft-Gault GFR <30 ml/min).

There are some important questions that arise from the enthusiastic introduction of dabigatran. Is it reasonable to expect that any new anticoagulant could be safely prescribed at a fixed dose with no anticoagulation monitoring? In our opinion, no.
Indeed, we would not expect any anticoagulant used in therapeutic doses to achieve a high level of safety.

As noted, this is because of the thin line that exists between therapeutic anticoagulation and the risk of bleeding. Therefore, we propose that all new anticoagulants should be backed up by independent and relevant drug information at their time of launch and the need to individualise dosage should be the expectation. Is dabigatran a breakthrough in anticoagulation? In our opinion, yes. Dabigatran is a novel anticoagulant and we believe if used appropriately will add to our ability to meet the needs of our patients. Dabigatran is not, however, a game changer. We should not discard warfarin simply on the grounds that it may be more difficult to use in favour of a drug where: reversibility in the presence of acute bleeding has not been established, the drug has wide variability in its exposure from any given dose, and is a candidate for many drug interactions.

We contend that a wide range of prescribed dabigatran doses across the population would be a good indicator of our success in selecting doses to meet our individual patients’ needs. If we do not monitor anticoagulation effects how do we really know we are meeting our patients’ needs? A blindfold is not what the best dressed practitioner should be wearing.

**Competing interests:** James Faed is a paid member of the Committee of Haematologists convened by PHARMAC to advise on the release of dabigatran in New Zealand.

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**References:**


