Commentary

Perspective on dabigatran etexilate dosing: why not follow standard pharmacological principles?

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Introduction

Individualized drug dosing is a major pursuit in clinical pharmacology. The principal covariates that determine drug maintenance dose rates are the renal and hepatic function of the individual [1]. The process of dose individualization is most clear for drugs that are renally cleared as there are established indices that can be employed to gauge renal function and thus guide dosing. Pharmaceutical companies tend to promote a 'one size fits all' approach in the interests of simplicity. In the following commentary, we review the approach to dabigatran etexilate, a renally eliminated drug that was initially promoted by its manufacturer as having 'one dose for all'. We aim to show that although guidelines have evolved that take renal function into account to some extent, these are applied insufficiently, not always logically and without consistency between indications. Guidelines have also eschewed monitoring of clotting function. This has happened despite the excellent pharmacokinetic and pharmacodynamic data (mostly from the manufacturer) that supports individualized dosing in relation to renal function using standard pharmacological principles, and anticoagulant monitoring in selected patients.

Dabigatran etexilate

Dabigatran etexilate is a new oral anticoagulant representing a new class, the direct thrombin inhibitors. It has achieved rapid marketing approval in many countries and enthusiastic early usage for the prophylaxis of thromboembolic events related to atrial fibrillation (AF) and orthopaedic surgery. Its purported benefits include the capacity to allow fixed dose regimens and the lack of a need for routine laboratory monitoring of coagulation [2]. It is thus supposedly much easier to use than warfarin, which has been the leading oral anticoagulant since it was introduced over 50 years ago. However, we believe this has

led to an oversimplification of the dosing recommendations by the manufacturers in the dabigatran etexilate datasheets, as we will discuss in further detail below. This in turn may result in an increased risk of bleeding in some and failure to control thrombosis in others.

The main problems with warfarin are well known and include complex pharmacokinetics (administered as a racemate; multiple metabolic elimination pathways including CYP2C9, which is subject to genetic polymorphism), pharmacodynamics affected by genetic polymorphism via VKORC1 and multiple pharmacokinetic and pharmacodynamic drug interactions. As a result the phenotype is monitored regularly, via the International Normalized Ratio (INR), with doses adjusted appropriately. However, there continues to be a concerning rate of serious bleeding events, contributing to warfarin's dubious distinction of consistently being amongst the most commonly implicated drugs associated with acute hospitalization for adverse drug events [3]. Consequently, a new 'warfarin' is needed, without the aforementioned problems. Dabigatran etexilate is postured as such an agent.

Dabigatran etexilate is described by its pharmaceutical company's researchers as having 'a predictable pharmacokinetic profile, allowing for a fixed dose regimen without the need for routine coagulation monitoring' [2]. However, this statement does not accurately reflect the comprehensive data provided by the same research group [4–6]. The narrow therapeutic index of this drug is a strong argument for an individualized dosing approach. Current guidelines from the manufacturer, Boehringer Ingelheim Limited (for example in the product datasheet in the United Kingdom) [7], recommend some individualization based on renal function, but do not go far enough, leaving some patients likely to be overdosed and some perhaps underdosed. Further, testing of clotting indices in clinical practice has been largely downplayed, despite evidence of strong concentration–effect relationships [2, 6].

Summary of pharmacokinetics (PK)

Dabigatran etexilate is a prodrug that has a low oral availability (F) of around 7% [8]. The low oral availability is because it is a substrate of intestinal epithelial P-glycoprotein (P-gp), an efflux transporter [7]. Dabigatran etexilate is thus vulnerable to interactions with P-gp inhibitors and inducers, to an extent that is potentially profound in a drug with such low oral availability. There are data to support this concern. In particular, the manufacturer's datasheet notes a number of P-gp inhibitors and inducers that alter dabigatran AUC by as much as 150% [7].

Following absorption, dabigatran etexilate is readily converted by plasma esterases to the active metabolite, dabigatran. Dabigatran has a steady-state volume of distribution of around 70 l and protein binding of around 35% [8]. Dabigatran undergoes predominantly renal clearance, with a proportionate decline in its clearance in relation to creatinine clearance (CL_{cr}) [6]. Compared with healthy subjects with mean CL_{cr} 103 ml min⁻¹, the dabigatran AUC(0,∞) (area under the concentration vs. time curve to infinity) was 1.5-, 3.2- and 6.3-fold greater for subjects with mean CL_{cr} of 67, 41 and 24 ml min⁻¹, respectively [6]. The terminal elimination half-life ($t_{1/2\beta}$) of dabigatran similarly increases with decreasing renal function, although not to as great an extent as would be expected based on the change in clearance alone. This is because the dabigatran volume of distribution at steady-state (V_d/F) also decreases markedly with renal dysfunction, although not proportionately as much as the decrease in CL_{cr} . Hence the $t_{1/2,z}$ for mean CL_{cr} 103, 67, 41 and 24 ml min⁻¹ was 14, 17, 19 and 28 h respectively [6]. The change in V_d/F with renal impairment, with a decrease of around 60%, is greater than expected, raising the possibility that an increase in oral availability may in fact be responsible. This might also explain why the decrease in apparent oral clearance (CL/F) is greater than expected in relation to renal impairment.

The extensive knowledge of the pharmacokinetics of dabigatran in renal impairment, along with clinical studies such as RE-LY, enables a target concentration approach to dosing. The 'typical atrial fibrillation patient' treated with 150 mg twice daily in RE-LY, using median values, was a 72-year-old, 80 kg male with a CL_{cr} of 69 ml min⁻¹ [9]. The plasma concentration range from the 10th percentile of the trough to the 90th percentile of the peak concentration is around 50–300 µg l⁻¹ [9], and might be considered a starting point for discussion regarding the desirable limits of exposure. A slightly narrower range of 75–240 µg l⁻¹, derived from the 10th percentile to 90th percentile for the AUC related to this typical AF patient [9] might be considered a useful target range. Simulations demonstrate that halving the dabigatran etexilate dose to 75 mg twice daily in patients with CL_{cr} of 29 ml min⁻¹ achieves exposure similar to that of 150 mg twice daily in the RE-LY study (median CL_{cr} 69 ml min⁻¹). These simulations also suggest

that similar targets can be achieved with a dose of 75 mg daily in patients with CL_{cr} of 15 ml min⁻¹ [10]. Data from Hariharan & Madabushi supports a similar fractional dose adjustment in relation to renal function impairment [11], although they conclude that 75 mg twice daily is appropriate for severe renal impairment (15–30 ml min⁻¹) based on a starting dose of 150 mg twice daily in patients with moderate renal impairment (30–50 ml min⁻¹).

These data support the standard principles of proportional dose reduction in relation to CL_{cr} for a predominantly renally eliminated drug. The ideal method of dose reduction is to establish a standard dose for a given CL_{cr} (e.g. 150 mg twice daily for CL_{cr} of 69 ml min⁻¹ from RE-LY), and then decrease the dose proportionally based on an estimate of CL_{cr} , such as the Cockcroft & Gault formula.

P-gp is an important contributor to renal clearance of drugs in general. Dabigatran etexilate is a P-gp substrate, but its active metabolite, dabigatran, while renally eliminated, is said not to be a substrate of P-gp [7]. The datasheet states that verapamil, a P-gp inhibitor, increased the AUC of dabigatran when administered 1 h prior to dabigatran etexilate, presumably as a result of intestinal P-gp inhibition. However, it had a negligible effect on dabigatran AUC when given 2 h after dabigatran etexilate, which is after absorption has been completed [7]. This suggests that renal tubular P-gp is not involved in the clearance of dabigatran.

Summary of pharmacodynamics (PD)

There is excellent correlation between many anticoagulant indices and dabigatran plasma concentrations (Table 1) [2]. Further, anticoagulant indices vary directly in time with dabigatran concentrations, consistent with a central compartment effect, which is expected given that its primary site of activity is in the blood. As a result, the expected effects on the anticoagulant indices can be read off the respective graphs for the target range of dabigatran plasma concentrations.

The current dabigatran etexilate datasheet dosing recommendations

The dosing recommendations in the UK dabigatran etexilate datasheets (Table 2) can be examined in relation to the pharmacokinetic and pharmacodynamic data discussed above.

The dosing recommendations take individual characteristics into account inconsistently between indications. This makes little sense when so much is known about the PK-PD relationship, and is likely to lead to excessive effect in those with impaired renal function, and perhaps

Table 1

Anticoagulant indices dabigatran concentrations

Anticoagulant index	Relationship with dabigatran plasma concentrations	Explained variance (r^2)	Notes
Ecarin clotting test (ECT) ratio	Linear	0.92	Not widely available.
Thrombin time (TT) ratio	Linear	0.86	TT very sensitive and exceeds maximum time of coagulometers at dabigatran concentrations achieved with standard doses.
Hemoclot® TT	Linear	0.99	Uses diluted plasma to overcome excessive sensitivity of traditional TT.
International normalized ratio (INR)	Linear	0.85	Flat slope of effect. Relatively insensitive compared to ECT and TT.
Activated partial thromboplastin time (aPTT) ratio	Curvilinear	0.85	Slope of effect flattens at higher concentrations. Relatively insensitive compared to ECT and TT.

Table 2

Current UK datasheet dosing recommendations [7]

	VTE prophylaxis	AF
Adults (>18 years)	220 mg once daily	150 mg twice daily
CL _{cr} 30–50 ml min ⁻¹	150 mg once daily	150 mg twice daily
CL _{cr} <30 ml min ⁻¹	Contraindicated	Contraindicated
Elderly >80 years	150 mg once daily	110 mg twice daily
Potent P-gp inhibitors	150 mg once daily*	Variable†
Other risk of bleeding	Not discussed	Consider 110 mg twice daily

*Amiodarone, quinidine, verapamil. †Amiodarone and quinidine, 150 mg twice daily; verapamil, 110 mg twice daily. AF, atrial fibrillation; CL_{cr}, creatinine clearance; P-gp, P-glycoprotein; VTE, venous thromboembolism.

insufficient effect in those with very good renal function. The following are some illustrative hypothetical examples.

For venous thromboembolism (VTE) prophylaxis, patient A, with a CL_{cr} of 51 ml min⁻¹, would likely have an AUC of dabigatran around two-fold higher than a 'reference patient' with a CL_{cr} of 100 ml min⁻¹ with both on 220 mg once daily. Similarly a 90-year-old, 50 kg woman, patient B, with an apparently 'normal' serum creatinine of 100 µmol l⁻¹ could receive a normal dose of 220 mg once a day (if a CL_{cr} was not estimated, as often happens when serum creatinine is within the normal range), and yet would have an AUC up to four-fold that of the 'reference patient'. Both of these patients would have excessive anticoagulation, and high risk of bleeding.

For prevention of stroke in atrial fibrillation (AF), patient A would receive a normal dose of 150 mg twice daily, resulting in a dabigatran AUC around 1.5-fold higher than the 'reference patient' with a CL_{cr} of 69 ml min⁻¹ (the standard dose was established in patients with a median CL_{cr} of 69 ml min⁻¹). If patient B was 79-years-old (just under the cut-off of 80 years) she would receive the full dose of 150 mg twice daily and have an AUC over two-fold higher than in a reference patient with CL_{cr} of 69 ml min⁻¹. Again, both of these patients would be at high risk of bleeding.

The actual data suggest that for a drug with a narrow therapeutic index and predominantly renal clearance, the dosing regimen should be appropriately adjusted for renal function, with laboratory indices of anticoagulant effect to assist dosing in high-risk subgroups. Such an approach could potentially offer a combination of greater therapeutic benefit and less risk of side effects to the patient. These must be important goals for both the drug manufacturer and the regulatory agencies.

Comment on published phase III trials of dabigatran etexilate in relation to dosing and CL_{cr}

The currently published dabigatran etexilate phase III trials are summarized in Table 3. For VTE prophylaxis following hip/knee joint replacement surgery involving patients with mean CL_{cr} >80 ml min⁻¹, dabigatran etexilate at 150 or 220 mg once daily was non-inferior to enoxaparin 40 mg daily but inferior to 30 mg twice daily, with no significant difference in major bleeding rates [12–14]. While there is no randomized controlled trial directly comparing these two enoxaparin regimens for VTE prophylaxis, the RE-MOBILIZE investigators have stated that their data suggest that enoxaparin 30 mg twice daily provides superior VTE prophylaxis to 40 mg daily [14]. The median CL_{cr} for all subjects in RE-LY was 69 ml min⁻¹ [9]. Compared with warfarin controlled to an INR of 2–3, patients in RE-LY had non-inferior efficacy and fewer major bleeding problems on 110 mg twice daily, and superior efficacy and equivalent major bleeding on 150 mg twice daily in the setting of AF [15]. In the RE-COVER study, patients with mean CL_{cr} of 105 ml min⁻¹ on 150 mg twice daily had non-inferior efficacy and fewer major bleeds in the setting of acute VTE treatment [16]. This result is similar to RE-LY with 110 mg twice daily with CL_{cr} of 69 ml min⁻¹ and might be expected as AUCs would be similar.

Table 3

Summary of dabigatran etexilate phase III studies

Trial	Anticoagulation indication	Dabigatran etexilate dosing	Control dosing	Participant age, mean (years)	Participant CL_{cr} , mean (ml min ⁻¹)	Primary outcome analysis (vs. control)	Bleeding analysis (vs. control)
RE-MODEL [12]	VTE prophylaxis post-KJR	150 mg or 220 mg daily	Enoxaparin 40 mg daily	68	?	VTE and all-cause mortality: non-inferior for both doses	Major bleeding: no significant difference for both doses Minor bleeding: analysis not given
RE-NOVATE [13]	VTE prophylaxis post-HJR	150 mg or 220 mg daily	Enoxaparin 40 mg daily	64	89	VTE and all-cause mortality: non-inferior for both doses	Major bleeding: no significant difference for both doses Minor bleeding: analysis not given
RE-MOBILIZE [14]	VTE prophylaxis post-KJR	150 mg or 220 mg daily	Enoxaparin 30 mg twice daily	66	83	VTE and all-cause mortality: inferior for both doses	Major bleeding: no significant difference for both doses Minor bleeding: analysis not given
RE-NOVATE II [22]	VTE prophylaxis post-HJR	220 mg daily	Enoxaparin 40 mg daily	62	97	VTE and all-cause mortality: non-inferior	Major bleeding: no significant difference Any bleeding: no significant difference
RE-LY [10, 15, 20]	AF	150 or 110 mg twice daily	Warfarin (INR 2–3)	71	73	Stroke or systemic embolism: non-inferior for both doses, superior for 150 mg twice daily	Major bleeding: superior for 110 mg no significant difference for 150 mg Any bleeding: superior for both doses
RE-COVER [16]	Acute VTE treatment	150 mg twice daily	Warfarin (INR 2–3)	55	105	VTE and all-cause mortality: non-inferior	Major bleeding: no significant difference Any bleeding: Superior

AF, atrial fibrillation; CL_{cr} , creatinine clearance; HJR, hip joint replacement; KJR, knee joint replacement; VTE, venous thromboembolism.

A more rational approach to dosing

Since the anticoagulant effect increases (directly in most cases) in relation to dabigatran concentrations and dabigatran concentrations increase proportionately as CL_{cr} declines, a clear dosage adjustment strategy is warranted. For similar concentrations and effects, the daily dose rate should be adjusted in relation to CL_{cr} . This is the conventional approach for drugs with renal elimination and a low therapeutic index, such as gentamicin and digoxin [1].

How should this be done with dabigatran etexilate? The simplest approach would be to replace the complex current dosing recommendations with a linear dose decrease in relation to impaired CL_{cr} . In other words, if normal CL_{cr} is 100 ml min⁻¹, then if CL_{cr} is 50 ml min⁻¹ or half normal, the dose rate should be half normal. This assumes that the drug is effectively cleared entirely renally unchanged. Although dabigatran is not entirely cleared renally unchanged (fraction excreted renally unchanged is 0.8), the remaining elimination is by glucuronidation [17]. The glucuronides are active [17], and themselves subject to renal and biliary elimination. Total dabigatran anticoagulant activity is therefore virtually entirely dependent on renal function. Therefore, for dose adjustment purposes, dabigatran could be treated as if its clearance is entirely dependent on renal function. As discussed earlier, data on plasma clearance of dabigatran in various degrees of renal impairment support this approach [6].

It should be noted that ‘normal’ doses of dabigatran have been ‘established’ in the patient groups who are to be treated, and are therefore based on different assumptions of starting CL_{cr} values for different indications. The RE-LY study involved patients with AF, whose mean age was 72 years and median CL_{cr} was 69 ml min⁻¹ [9]. In the RE-COVER study, which was for VTE, the mean age was 55 years and the mean CL_{cr} was 105 ml min⁻¹. It could therefore be argued that for AF the reference CL_{cr} is around 70 ml min⁻¹, while for VTE it is around 100 ml min⁻¹. Dose rate adjustment should proceed as follows:

$$\text{Dose rate Patient (VTE)} = \frac{\text{Normal dose rate (Patient's } CL_{cr}/100)}{}$$

$$\text{Dose rate Patient (AF)} = \frac{\text{Normal dose rate (Patient's } CL_{cr}/70)}{}$$

A patient with VTE and a CL_{cr} of 50 ml min⁻¹ would therefore have a dose rate of 50% of the normal dose rate, while a patient with AF and a CL_{cr} of 50 ml min⁻¹ would have a dose rate of 70% of the normal dose rate. In the case of AF, a patient with a CL_{cr} of 100 ml min⁻¹ could theoretically have an increase in dose of 4/3 or 1.33 of the normal dose rate in order to achieve the same AUC as a patient with a CL_{cr} of 70 ml min⁻¹.

It is important to note that the precise proportional adjustment of the dose rate is restricted by the available

dosage strengths and formulations. This is relevant in the case of dabigatran etexilate where the available strengths from the manufacturer are capsules of 75, 110 and 150 mg. In specific localities, these may be further limited by local regulatory bodies. An example is the Food and Drug Administration (FDA), which in 2010 approved the 75 and 150 mg, but not the 110 mg capsule for use in AF in the United States [18]. This is in contrast to other localities, such as the United Kingdom, that have approved all three strengths for AF [7]. While the FDA concluded that there was inadequate clinical evidence from RE-LY to approve the 110 mg strength for AF, a pharmacological approach based on target dabigatran concentrations would advocate the availability of all three strengths to allow for flexibility with individualized dosing.

Can more improvements be made?

The above approach assumes that no end-points of anti-coagulant effect are routinely being monitored, which is the current recommendation. This is based on major phase III studies that did not employ routine coagulation testing as part of dabigatran etexilate use, with outcomes that have been comparable with conventional management (e.g. warfarin with INR monitoring for AF). However, we argue that many patients included in these trials, such as those with moderately impaired renal function, will have had very high dabigatran concentrations, and consequently been at higher risk of haemorrhage as a result of the current drug company's dosing guidelines. Examples (patients A and B) are given above. Further, change in renal function over time may also be important, especially in AF, where patients are likely to be anti-coagulated for years.

As a result of the very strong relationship between dabigatran plasma concentrations and anticoagulant effects, monitoring of anticoagulant effects could assist in the management of patients at higher risk of thrombotic episodes and/or haemorrhage. This includes patients with: severe renal impairment, age ≥ 75 -years-old [19], other reasons for altered clotting and co-treatment with drugs with P-gp interactions. Laboratories should be encouraged to set up the Ecarin Clotting Test (ECT) or Hemoclot® Thrombin Time (TT) assays because of the extremely strong linear relationship with dabigatran concentrations. A target range for the Hemoclot® TT, which corresponds to dabigatran plasma concentrations of 75–240 $\mu\text{g l}^{-1}$, is 55 to 65 s [2]. Feedback and appropriate dose adjustment to achieve such target end points would increase the likelihood of antithrombotic efficacy while decreasing the risk of excessive bleeding. Such an approach lends itself to further clinical trials.

Finally, a twice daily regimen is likely to be better than a once daily regimen for patients, since it results in lower peak and higher trough concentrations for equivalent

Table 4

Proposed dabigatran etexilate dosing recommendations

CL _{cr} (ml min ⁻¹)	VTE prophylaxis dose rate	AF dose rate
≥ 80	220 mg daily	?220 mg twice daily
50–<80	150 mg daily	150 mg twice daily
30–<50	75 mg daily	75 mg twice daily
15–<30	?75 mg alternative days	75 mg daily

AF, atrial fibrillation; CL_{cr}, creatinine clearance; VTE, venous thromboembolism.

AUCs across 24 h. This may reduce any bleeding risk associated with peak concentration effect and increase beneficial effects because of higher trough values, at some expense in compliance [20]. Further, while not necessarily pharmacokinetically relevant, twice daily dosing would mean a consistent dosing frequency across indications.

Summary of a potential dosing algorithm

Based on this discussion, we propose the following dosing algorithm:

- 1 Estimate the patient's CL_{cr}.
- 2 For VTE prophylaxis the standard dose in normal renal function is 220 mg once daily or alternatively 110 mg twice daily. These dose rates should be decreased linearly for decreases in CL_{cr}, assuming a normal CL_{cr} of 100 ml min⁻¹ i.e. if estimated CL_{cr} is 50 ml min⁻¹ (half normal), then the dose should be half normal.
- 3 For AF, the standard dose in patients with CL_{cr} of around 70 ml min⁻¹ is 150 mg twice daily. This dose rate should be adjusted linearly for decreases in CL_{cr}, but assuming the 'normal' CL_{cr} is 70 ml min⁻¹, i.e. if estimated CL_{cr} is 50 ml min⁻¹, then the dose should be 2/3 normal.
For steps 2 and 3, Table 4 is a useful starting point, based on popular divisions of CL_{cr}, for those unable to undertake proportional dosing reduction.
- 4 Doses should be rounded to fit with available dosage strengths.
- 5 Monitor renal function, especially where the patient is at higher risk of deteriorating renal function [21].
- 6 Consider further dose decreases in patients on strong P-gp inhibitors (e.g. amiodarone) and those at increased risk of bleeding (e.g. previous gastrointestinal bleeding, age ≥ 75 -years-old).
- 7 Anticoagulant tests can be used to check for excessive effect and should be conducted in patients in whom there might be concern, e.g. CL_{cr} bordering around 30 ml min⁻¹, potential P-gp drug interactions. Where appropriate tests are not available (e.g. ECT), plasma

dabigatran concentrations (suggested target range for AF of 75–240 µg l⁻¹) can be measured if a validated assay is available.

Competing interests

There are no competing interests to declare.

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