Commentary

Optimizing the dose of dabigatran etexilate

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The benefit : risk ratio for an oral anticoagulant is crucial, since the consequences of thromboembolic events on the one hand, and intra- or extra-cranial haemorrhage on the other, are potentially very serious. Therefore, the target profile for any new oral anticoagulant should include 'readily predictable dosage'. To achieve this, the product's pharmacokinetics should exhibit low variability with no important effects of age, body weight, genetic polymorphisms, stereo-isomerism, food ingestion, organ dysfunction and few if any clinically important drug–drug interactions.

Warfarin fails on just about all counts with the result that intra- as well as inter-individual dosage requirements are highly variable and require close monitoring. Patients with atrial fibrillation (AF) participating in clinical trials are known to be outside the target range of INR 2–3 more than a third of the time [1] and, due to a multitude of factors, the figure is no doubt much higher than this in the general population of patients prescribed warfarin. In a study of 472 elderly patients, of whom 32% were >80 years of age, the cumulative incidences of major haemorrhage for patients >80 and <80 years of age were 13.1 and 4.7 per 100 person-years respectively ($P = 0.009$) [2].

With the advent of new anticoagulants, notably inhibitors of thrombin (e.g. dabigatran) and Factor Xa (e.g. rivaroxaban and apixaban), we may expect warfarin to be replaced by safer medicines. Indeed, reasonable criteria for licensing such an agent today should include at least non-inferior efficacy to warfarin and superiority with respect to safety. However, such comparisons do not go far enough. Treatment should be optimal for the individual.

The thrombin inhibitor dabigatran is formed rapidly by a serum esterase after oral administration and absorption of its prodrug dabigatran etexilate. In Europe it is licensed for primary prevention of venous thromboembolism in adults who have had elective total hip or knee replacement surgery and for reducing the risk of stroke and systemic embolism in patients with non-valvular AF. In the USA it is licensed only for use in patients with AF. Despite very low bioavailability (4–7%), pharmacokinetic parameters ($C_{\max}$ and AUC), exhibit low to moderate variability

(CVs of 27–43%) in healthy volunteers and concentrations are proportional to dose [3]. Renal clearance accounts for most of the total clearance of dabigatran and its active acyl conjugates and glomerular filtration rate is the main source of variation. In patients with mild (CL_{cr} 50–80 ml min⁻¹), moderate (30–50 ml min⁻¹) or severe (15–30 ml min⁻¹) renal impairment, increases in mean $C_{\max}$ were respectively 1.1-, 1.7- and 2.1-fold those of controls and corresponding increases in mean AUC were 1.5-, 3.2- and 6.3-fold [4].

In the pivotal (RE-LY) trial of dabigatran in non-valvular AF, the incidence of stroke or systemic embolism was lower with dabigatran 150 mg twice daily ($n = 6076$) than with warfarin ($n = 6022$) with a relative risk of 0.66 (95% CI 0.53, 0.82); $P < 0.0001$ for superiority [5]. However, there was no significant difference in the incidence of major bleeding episodes (3.31% vs. 3.57%, $P = 0.32$) and a substantial proportion of these were life threatening. The incidence of bleeding was actually lower with dabigatran than warfarin in patients <75 years of age (2.12% vs. 3.04%, $P < 0.001$) but there was a clear trend to a higher incidence in those aged >75 years (5.10% vs. 4.37%, $P = 0.07$) [6]. A lower dose of 110 mg twice daily ($n = 6015$), (licensed in the UK but not in USA) caused less haemorrhage but its efficacy in preventing stroke or systemic embolism was not superior to that of warfarin. Taking into account that the incidence of haemorrhage on warfarin was higher than expected, perhaps due to the large number of patients also taking aspirin [7], the safety of the recommended dose of dabigatran in the elderly must be seriously questioned.

The risk of haemorrhage is well recognized and in a recent Drug Safety Update issued by the MHRA [8], we were informed of a number of cases of serious and fatal haemorrhage in elderly patients with renal impairment treated with dabigatran etexilate. In the USA, there were more reports of bleeding with dabigatran than for warfarin in the first quarter of 2011 and many of the events involved intracranial haemorrhage. Even allowing for the fact that serious adverse events are more likely to be reported for a new drug than an old one, this suggests that these patients were being overdosed. Very recently, the CMPH issued a

statement recommending updating the product information to give clearer guidance to prescribers and patients on reducing and managing the risk of bleeding but the statement did not amount to more than re-emphasizing the current recommendations [9].

If it is possible to achieve a safety profile with dabigatran superior to that of warfarin in the elderly, how might this be achieved? It is recommended that renal function be assessed in all patients before starting treatment and the MHRA advise that it should be checked at least annually in patients of >75 years or those with a suspected decline in renal function. In their 'Perspective on dabigatran etexilate dosing – why not follow standard pharmacological principles?', in this issue of the Journal, Chin *et al.* propose dosing algorithms for dabigatran based on estimated renal function [10]. Furthermore, since dabigatran is a substrate for the intestinal efflux transporter P-glycoprotein (P-gp), they propose adjustments for concomitant medication with strong P-gp inhibitors and also for those at increased risk of bleeding, e.g. previous gastrointestinal bleeding. These proposals make good sense but do they go far enough? Chin *et al.* suggest monitoring for excessive effects in higher risk patients. It seems to me that this is the critical issue which must be addressed.

In a population pharmacokinetic analysis based on a total of 27 706 samples from 9522 patients, as expected, CL_{cr} was an important covariate for apparent clearance of dabigatran but other covariates with significant effects on apparent clearance included age, gender, heart failure and the ethnic subgroup 'South Asian' [11]. Bioavailability was significantly affected by concomitant medication with proton pump inhibitors, amiodarone and verapamil. It was concluded that none of the covariates except renal function merited dosage adjustment but what of the cumulative effects of combinations of these factors in individual patients?

A study performed in healthy young and elderly (≥ 65 years) subjects showed that prolongation of ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) correlated with plasma concentrations, with the ECT directly proportional to prevailing plasma concentration [12]. It was therefore claimed that the pharmacokinetics and resultant anticoagulant effect are predictable and hence there is no need to monitor therapy. On the basis that a new drug is guilty until proven otherwise, and bearing in mind that there is currently no known antidote to dabigatran, exploration of the variability in anticoagulant function must be explored.

Of the possible tests available, direct monitoring of thrombin inhibition in the presence of dabigatran is probably the most rational approach. The calibration curve of the HEMOCLOT thrombin inhibitor assay has been shown to be linear with dose over a wide concentration range with good precision and low bias of coagulation times between laboratories [13]. The test is rapid and could easily become routine. A recommended range of coagulation

time would need to be established in a large population, taking into account rates of haemorrhage in different age groups. It will be important to establish whether age *per se* increases the risk of gastrointestinal haemorrhage or whether the excess incidence in the elderly is explained entirely by overdosage associated with reduced renal clearance. For the majority of patients, it would probably only be necessary to perform the test once or twice, soon after starting therapy and again if risk factors change such as a decline in renal function or addition of an interacting medication, or in the event of gastrointestinal disease. It would undoubtedly be less demanding than monitoring warfarin therapy but might achieve the optimal safety that patients treated with dabigatran have the right to expect.

Competing Interests

The author has completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares 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 previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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