Dabigatran elimination: is haemodialysis effective?
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Dabigatran, a direct thrombin inhibitor with oral bioavailability via its pro-drug dabigatran etexilate, has been approved in the US and Europe for both the prevention of stroke and thrombo-embolic disease in patients with non-valvular atrial fibrillation (AF), and for the prevention of venous thromboembolism after hip and knee replacement in Europe. While the traditional oral anticoagulant (OAC) warfarin reduces risk of stroke by approximately 2/3 in patients with AF (1), it is underutilised in populations in whom OAC is indicated (2), and often only achieves suboptimal anticoagulation according to time in the therapeutic range based on international normalized ratio (INR) testing (3).

Dabigatran has recently emerged as an alternative to warfarin due to its rapid onset of action, predictable pharmacodynamics and pharmacokinetics, and lack of need for regular blood monitoring (4). The pivotal trial for dabigatran was the RE-LY trial (5), which randomised 18,113 patients with non-valvular AF at risk of stroke to dabigatran (either at a dose of 110 mg or 150 mg bd) or warfarin. The rate of the primary outcome of stroke or systemic embolism was significantly reduced for patients on dabigatran 150 mg bd compared to warfarin (1.11% vs. 1.69%/year); however, the rate of major bleeding at this dose (3.11%/year) was not significantly different from that of warfarin (3.36%/year).

A key limitation to dabigatran is that there is no reversal agent commercially available in situations such as emergent surgery, major bleeding or overdose (6), though there have been reports on the utility of haemostatic non-specific reversal agents such as prothrombin complex concentrates and recombinant activated factor VII (4, 7), as well as activated charcoal (8), plasmapheresis (9) and haemodialysis (10-13).

One previous study (10) included six patients with end-stage renal failure who were given a single 50 mg dose of dabigatran at the commencement of a 4 hour (h) dialysis session. Dialysis removed 62-68% of dabigatran (pre to post dialysis filter concentration); however, the fraction cleared from the plasma was not reported.

In the present issue of Thrombosis and Haemostasis, Khadzhynov et al. (14) report on the elimination of dabigatran by haemodialysis in a single-centre phase I study in patients with end stage renal disease (ESRD), which perhaps represents an ideal human model to evaluate the effects of dialysis on dabigatran for a number of reasons.

First, these patients already have an arterio-venous fistula (AVF) in situ (which both reduces risk of central catheterisation whilst anticoagulated, and also allows for assessment of a broader range of dialysis blood flows). Second, as dabigatran is primarily cleared by the kidneys (~80%) (15), and the patients studied had minimal or no residual renal function, renal clearance of dabigatran was minimal and thus unlikely to confound the assessment of the effectiveness of dialysis on dabigatran elimination.

In a total of seven patients with ESRD and functioning AVF on a thrice weekly haemodialysis regimen, elimination rates of dabigatran from plasma were assessed after administration of multiple doses timed to achieve plasma concentrations similar to those reported in patients without ESRD taking dabigatran 150 mg bd for AF. The multiple dosing schedule also allowed for dabigatran distribution between the central and peripheral compartments, in turn allowing for assessment of redistribution from the interstitium to the central compartment after the completion of dialysis. Pharmacokinetic and pharmacodynamic assessments were performed at a targeted blood flow of 200 ml/minute (min) (to approximate maximal blood flow during central catheter dialysis, as would be performed in emergency situations) and 400 ml/min, to assess the influence of targeted blood flow on elimination rates. Haemodialysis characteristics were further optimized by using high dialysate flow rates and high flux filters with an extra-large surface.

The key findings from the study by Khadzhynov et al. (14) are as follows: (i) a single 4 h haemodialysis session cleared 48.8% of plasma dabigatran at a blood flow of 200 ml/min and 59.3% at 400 ml/min, (ii) the anticoagulant activity of dabigatran was linearly related to dabigatran plasma concentrations, and (iii) a 7.5-15% redistribution of dabigatran was noted after the end of dialysis.

The authors are to be commended on designing and performing this study on a highly relevant topic and taking into account clinically important aspects such as the assessment of dialysis blood flow at rates comparable to that achievable by central catheter dialysis, the multiple dosing schedule thereby allowing to achieve dabigatran plasma concentration resembling those commonly seen in patients without ESRD, and assessing redistribution effects, as well as assessment of (both plasma and blood) dabigatran concentration and anticoagulant effect at multiple time points including during the redistribution phase.

Important limitations of this trial include the small sample size of only seven

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patients, which to some extent may account for the relatively large variation in redistribution rates post-dialysis. Notably the dabigatran dosing schedule for patients with ESRD, and safety-tolerability of dabigatran in ESRD should not be extrapolated into clinical practice from this cohort of seven patients. Whether the pharmacodynamic and pharmacokinetic profile of dabigatran elimination and redistribution in patients without ESRD differs from that described in the present study remains to be determined. Larger prospective studies in non-ESRD cohorts would be useful to address some of these issues.

Other important clinical issues that require consideration include the risk of central venous catheterisation in fully anticoagulated patients, the unknown effect of dialysis on supra-normal levels of dabigatran (e.g. in overdose setting), whether a ~50% reduction in plasma concentration will correlate with clinical improvement (regarding haemostasis) in emergent situations, and the implications for the overall cost-benefit of dabigatran vs. warfarin should a fraction of the ~3% of patients with major bleeding per year on dabigatran require emergent dialysis.

With an expanding number of patients on dabigatran (the US Food and Drug Administration reported that from October 2010 to August 2012 3.7 million prescriptions for dabigatran were dispensed), major bleeding requiring reversal will be inevitable. Given there is no reliable reversal agent for dabigatran, this study strengthens the potentially important role that dialysis may play for patients who require emergent reversal of effect while on therapeutic anticoagulation with dabigatran.

Conflicts of interest
None declared.

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