Initial experience with dabigatran etexilate at Auckland City Hospital

We write with reference to the inclusion of dabigatran etexilate (Pradaxa)—a pro-drug of dabigatran—on the pharmaceutical schedule in New Zealand without restriction on 1 July 2011.1

Dabigatran is a reversible thrombin inhibitor licensed for the use of stroke prevention in atrial fibrillation (AF) granted on the basis of data from the RE-LY study2 and is an alternative to anticoagulation with warfarin. Due to its novelty, the place of dabigatran in the management of AF is not fully established and, importantly, there are no specific antagonists to dabigatran-induced bleeding.

Warnings at the end of 2011 from the Therapeutic Goods Administration,3 Food and Drugs Administration,4 and Medicines and Healthcare products Regulatory Agency5 all highlight at risk patients of drug-induced bleeding (patients >75 years and those with renal impairment). Patients given drugs in everyday practice may differ from the demographic of patients recruited for drug trials upon which licensing decisions are based.

We sought to determine whether the initial cohort of patients admitted to Auckland City Hospital (ACH) on dabigatran, for 6 months July to December, 2011, mirrored the demographic of the RE-LY study participants.

The notes of all patients admitted through the Adult Emergency Department and the Admission and Planning Unit of ACH while taking dabigatran were reviewed and their details recorded for the six month time frame. The information was recorded irrespective as to whether the dabigatran was the cause of admission or just an association.

In all cases patient demographics were recorded (that were available) in an anonymised fashion, including age; weight (kg); renal function (creatinine clearance calculated by Cockroft-Gault formula, CrCl, ml/min); indication for dabigatran use and dosage used; presence of haemorrhage; and concomitant drug use. Data are presented as mean values ± standard error and shown against the RE-LY figures.

Seventy nine patients (33 female) taking dabigatran were admitted through AED/APU at Auckland City Hospital between July and December 2011. All patients had AF as the indication for dabigatran therapy. The mean age of patients was 76 ± 1.7 (range: 19–93, median 84) years; weight 77 ± 2.3 (range: 38-126, median 73) kg; CrCl 67 ± 5.9 (range: 12-137, median 61) ml/min. The mean RE-LY equivalents are: age 71 years; weight 82.5 kg; CrCl not stipulated in article (patients with CrCl <30 ml/min were excluded from the trial).

The ACH patients were on a mean 6.0 ± 0.8 other medications in addition to their dabigatran. Seven of the 79 patients were on an antiplatelet agent (aspirin or clopidogrel) in addition to dabigatran and one patient was on warfarin plus dabigatran plus aspirin. Sixteen patients were admitted with dabigatran-induced bleeding (11
gastrointestinal bleed; 4 haematuria; one haematoma). Three patients had their emergency surgery delayed (2 fractures; one ischaemic limb) because of inability to reverse dabigatran-bleeding.

These initial data show that dabigatran is being prescribed to patients who differ from those enrolled in the original trial. This may have consequences for drug pharmacokinetics and the incidence of adverse effects, including bleeding the management of which remains uncertain.

Dabigatran is predominantly excreted renally and patients with renal impairment are at risk of enhanced bleeding. Patients with CrCl < 30 were excluded from the RE-LY study (six of our patients had this degree of impairment) and recent warnings suggest that the drug should be used with caution if CrCl is between 30-50 ml/min (22 of our patients). Our patients were generally less heavy than those in RE-LY. The effect of weight on dabigatran kinetics is not known.

Dabigatran is not metabolised by the cytochrome P450 system but is excreted by p-glycoproteins and inhibitors of this system (e.g. amiodarone) can increase its bioavailability. Dabigatran was coprescribed with a mean 6 other medications and future experience will inform us of important drug interactions. Seven of our patients were prescribed an antiplatelet agent in addition to dabigatran. Such concurrent use markedly enhances bleeding tendency in an expected pharmacodynamic manner without good evidence of enhanced patient outcomes.

In conclusion, we have found that in its first 6 months of use, in the catchment area of ACH, dabigatran has been used in a group of patients that differs from those recruited in studies. Our patients were older, of lower weight and with a lower CrCl than the RE-LY-study patients. Dabigatran was also used in patients on multiple other drugs, including antiplatelet agents, and clinicians should be vigilant for potential drug interactions (whether pharmacokinetic or pharmacodynamic) and report any concerns to the Centre for Adverse Reactions Monitoring. Dabigatran use resulted in the delay of emergency surgery in three patients.

While it may not be surprising that drugs are used outside of their evidence-base, we urge caution in the future prescribing of this novel anticoagulant (that has no antagonist or means of monitoring) in patient groups that may be at enhanced risk of drug-induced haemorrhage.

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