Letter to the Editors

Rifampicin and dabigatran etexilate: a place for laboratory coagulation monitoring

Paul K. L. Chin, Murray L. Barclay & Evan J. Begg

Department of Clinical Pharmacology, Christchurch Hospital, Christchurch, New Zealand

The paper by Hartter *et al.* on the interaction between dabigatran etexilate and rifampicin [1] is an important addition to the published data on drug–drug interactions involving dabigatran etexilate. Dabigatran etexilate is a substrate of intestinal P-glycoprotein (P-gp). Compared with dabigatran etexilate alone, the co-administration of rifampicin, a P-gp inducer, was associated with a 67% reduction in dabigatran AUC(0,∞). Consequently, Hartter *et al.* recommend that this drug–drug interaction be managed by avoiding the combination of dabigatran etexilate and rifampicin or any other P-gp inducers, e.g. carbamazepine. We would like to suggest an alternative management strategy to avoidance of such drug combinations.

The interaction with rifampicin or other P-gp inducers could be managed by laboratory coagulation monitoring and appropriate dose adjustment of dabigatran. As Hartter *et al.* point out, rifampicin also has a significant impact on warfarin concentrations. O'Reilly demonstrated a reduction in steady-state plasma warfarin concentrations of around 85% [2]. Instead of avoidance, the combination of rifampicin and warfarin is managed by monitoring the International Normalized Ratio (INR) and appropriate warfarin dose adjustment.

It may not be immediately clear how laboratory coagulation monitoring should proceed, given that none of the phase III studies of dabigatran etexilate used targeted dosing based on coagulation assay values. However, published data show excellent correlation between dabigatran concentrations and various coagulation assays, e.g. Hemo-clot® Thrombin Time (HTT, $r^2 = 0.99$) [3]. Pharmacokinetic data from the RE-LY study of dabigatran etexilate for atrial fibrillation revealed plasma dabigatran concentrations of 50–300 µg l⁻¹ [4]. Using these concentrations, target values for anticoagulation may be read off the correlation graphs, e.g. 40–75 s for HTT.

Laboratory coagulation monitoring is also likely to be useful for other pharmacokinetic drug–drug interactions involving dabigatran. The European Union label for dabigatran etexilate currently includes a confusing list of

dosing recommendations for various pharmacokinetic interactions [5]. For example, rifampicin is 'not recommended' because of a 67% reduction in concentrations, whereas the guidance for amiodarone, which is associated with a 60% increase in concentrations, is 'use with caution and assess bleeding risk' without any suggestion for dose adjustment. Further, how one should manage the co-administration of multiple drugs affecting dabigatran concentrations is unclear. Dose adjustment of dabigatran etexilate based on feedback from laboratory coagulation monitoring seems a reasonable answer to these concerns, and would allow more patients to benefit from this drug.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare 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.

REFERENCES

- 1 Hartter S, Koenen-Bergmann M, Sharma A, Nehmiz G, Lemke U, Timmer W, Reilly PA. Decrease in the oral bioavailability of dabigatran etexilate after co-medication with rifampicin. *Br J Clin Pharmacol* 2012; 74: 490–500.
- 2 O'Reilly RA. Interaction of chronic daily warfarin therapy and rifampin. *Ann Intern Med* 1975; 83: 506–8.
- 3 van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, Clemens A. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010; 103: 1116–27.

- 4 Lehr T, Haertter S, Liesenfeld KH, Staab A, Clemens A, Reilly PA, Friedman J. Dabigatran etexilate in atrial fibrillation patients with severe renal impairment: dose identification using pharmacokinetic modeling and simulation. *J Clin Pharmacol* 2011 (in press). doi: 10.1177/0091270011417716.
- 5 Huisman MV, Lip GY, Diener HC, Brueckmann M, van Ryn J, Clemens A. Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. *Thromb Haemost* 2012; 107: 838–47.

RECEIVED

23 May 2012

ACCEPTED

23 June 2012

ACCEPTED ARTICLE PUBLISHED ONLINE

1 August 2012

CORRESPONDENCE

Dr Paul K. L. Chin, Department of Clinical Pharmacology, Christchurch Hospital, 2 Riccarton Avenue, Christchurch 8140, New Zealand.

Tel.: +64 336 4640 extension 88354

Fax: +64 3364 1003

E-mail: paulc@cdhb.health.nz