Letter to the Editors

Response to the letter by Dr Chin and co-workers

Sebastian Härtter,¹ Michael Koenen-Bergmann,² Ashish Sharma,¹ Gerhard Nehmiz,¹ Ute Lemke,¹ Wolfgang Timmer³ & Paul A. Reilly⁴

¹Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, ²Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, ³CRS Mannheim GmbH, Mannheim, Germany and ⁴Boehringer Ingelheim Pharma, Ridgefield, CT, USA

Dr Chin and co-workers [1] have described an approach to addressing drug interactions using adapted dosing which targets a presumed therapeutically beneficial plasma concentration range. They also proposed this approach for the described interaction between the prototypic CYP3A4/P-gp inducer rifampicin and the direct reversible thrombin inhibitor dabigatran etexilate.

We would like to raise our concerns over this approach for the following reasons. Firstly we demonstrated a reduction in exposure to one-third (or in other words by about two-thirds of the reference exposure) in a formally designed drug–drug interaction study [2], which would imply that the dose would have to be increased by a factor of ~3. This would require a very large dose of 3×150 mg twice daily or 900 mg day^{-1} , which is a dosing regimen that has never been given to any human. Furthermore, one also does not have data using rifampicin concomitantly with dabigatran etexilate in patients, when they often will not have been fasting (as done in the phase I study) and would be expected to take all of their medications at the same time of day (again different from the phase I study).

More importantly, from a clinical point of view, rifampicin is not a chronic treatment and, after cessation of rifampicin therapy, the inductive effect will decay over time. This would preferably require a tiered dose reduction. There is, however, the possibility that this dose adaptation after rifampicin treatment cessation would not be accomplished appropriately or could even be completely forgotten. Since the prevention of strokes is the primary goal of the administration of any anticoagulant, prior to the use of a simple dosing paradigm as proposed in the comment of Dr Chin and coworkers [1], we strongly suggest that human patient data be developed.

Thus, we are of the strong opinion that the current label recommendation warning against concomitant dabigatran etexilate and rifampicin use is appropriate in order to ensure the therapeutic efficacy and safety of dabigatran etexilate.

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 SH, MKB, AS, GN, UL and PR had support from Boehringer Ingelheim for the submitted work and SH, MKB, AS, GN, UL and PR are employees of Boehringer Ingelheim. WT has no competing interests to declare.

REFERENCES

- 1 Chin PKL, Barclay ML, Begg EJ. Rifampicin and dabigatran etexilate: a place for laboratory coagulation monitoring. *Br J Clin Pharmacol* 2013; 75: 554–5.
- 2 Härtter 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.

RECEIVED

6 July 2012

ACCEPTED

24 July 2012

ACCEPTED ARTICLE PUBLISHED ONLINE

1 August 2012

CORRESPONDENCE

Dr Sebastian Härtter, Boehringer Ingelheim Pharma GmbH & Co. KG, Translational Medicine, Birkendorfer Strasse 65, 88397 Biberach/Riss, Germany.
Tel.: +49 73 5154 5950
Fax: +49 735 1549 0170
E-mail: sebastian.haertter@boehringer-ingelheim.com