LETTERS

Letters to the Editor

Treating patients on new anticoagulant drugs

Aust Prescr 2017;40:46–7
http://dx.doi.org/10.18773/austprescr.2017.021

I agree with the authors of the new oral anticoagulants article that the drugs should be viewed 'as useful arrows in the prescriber's quiver of oral anticoagulants' rather than to replace warfarin.[1] However a previous *Australian Prescriber* comment[2] did not adequately address the practical aspects of reversal of the newer anticoagulants.

Significant concerns have been raised about how the manufacturer of dabigatran may have withheld data in the RE-LY trial,[3] with the possibility that issues about the bleeding risk were far greater than were acknowledged. This was particularly in light of the drug's 'fickle pharmacokinetics' resulting in highly variable plasma concentrations[4] and differences in how the different drug regulators managed this issue.[5]

Trials involving dabigatran versus warfarin may have underestimated major bleeding rates,[6] and possibly the risk of gastrointestinal bleeding related to dabigatran and rivaroxaban compared to warfarin[7] despite their touted safety profile.

There was also controversy with the ROCKET-AF trial of rivaroxaban,[8] where serious allegations that a defective point-of-care device was used in the warfarin arm. This could have potentially affected the trial results and emphasises the importance of post-marketing trials to authenticate company-sponsored trials used to support the drug's approval.

Even idarucizumab, the monoclonal antibody antidote to dabigatran (both from Boehringer Ingelheim), comes with a certain caveat not widely known – the median time to bleeding cessation was 11.4 hours for those with overt, uncontrollable, or life-threatening bleeding that was judged by the treating clinician to require a reversal agent.[9] Hopefully, whatever a 'life-threatening bleed' is, 12 hours delay (before bleeding stops) is consistent with meaningful life.

Although the effect of reversal is up to 24 hours, 'subsequent increases in dabigatran concentrations that occurred 12 hours after the administration of idarucizumab in six patients and 24 hours after the administration of idarucizumab in 16 patients were also evident by increases in the clotting times and may reflect the redistribution of extravascular dabigatran into the intravascular compartment'.[9] Therefore the anticoagulation effect of dabigatran, taking 2–4 days post cessation to be safe from significant bleeding or major surgery, may still relapse 24 hours after the last dose of idarucizumab.

Conversely, warfarin can be reversed by vitamin K, prothrombin complex concentrate or fresh frozen plasma within 15 minutes to six hours.[10]

Clinicians and patients should be informed of these facts before embarking on therapy involving the newer anticoagulants.

Shyan Goh
Orthopaedic surgeon
Meadowbrook, Qld

REFERENCES

1. Chin PK, Doogue MP. Long-term prescribing of new oral anticoagulants. Aust Prescr 2016;39:200-4. http://dx.doi.org/10.18773/austprescr.2016.068
2. Idarucizumab. Aust Prescr 2016;39:183. http://dx.doi.org/10.18773/austprescr.2016.076
3. Cohen D. Dabigatran: how the drug company withheld important analyses. BMJ 2014;349:g4670. http://dx.doi.org/10.1136/bmj.g4670
4. Charlton B, Redberg R. The trouble with dabigatran. BMJ 2014;349:g4681. http://dx.doi.org/10.1136/bmj.g4681
5. Moore TJ, Cohen MR, Mattison DR. Dabigatran, bleeding, and the regulators. BMJ 2014;349:g4517. http://dx.doi.org/10.1136/bmj.g4517
6. Wang SV, Franklin JM, Glynn RJ, Schneeweiss S, Eddings W, Gagne JJ. Prediction of rates of thromboembolic and major bleeding outcomes with dabigatran or warfarin among patients with atrial fibrillation: new initiator cohort study. BMJ 2016;353:i2607. http://dx.doi.org/10.1136/bmj.i2607
7. Abraham NS, Singh S, Alexander GC, Heien H, Haas LR, Crown W, et al. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. BMJ 2015;350:h1857. http://dx.doi.org/10.1136/bmj.h1857
8. Cohen D. Rivaroxaban: can we trust the evidence? BMJ 2016;352:i575. http://dx.doi.org/10.1136/bmj.i575
9. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511-20. http://dx.doi.org/10.1056/NEJMoa1502000
10. Tran HA, Chunilal SD, Harper PL, Tran H, Wood EM, Gallus AS; Australasian Society of Thrombosis and Haemostasis (ASTH). An update of consensus guidelines for warfarin reversal. Med J Aust 2013;198:198-9. http://dx.doi.org/10.5694/mja12.10614

Paul Chin and Matthew Doogue, the authors of the article, comment:

Dr Goh raises important concerns about the reversal of anticoagulation with the new oral anticoagulants in the setting of bleeding, particularly in relation to dabigatran.

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

Dabigatran therapy was found to be non-inferior to warfarin in terms of major bleeding risk and mortality in the randomised controlled trials that preceded the availability of the reversal agent, idarucizumab.[1-3] It is possible that idarucizumab will improve the safety of dabigatran to the extent that it is superior to the safety of warfarin, for example by rapid reversal before acute surgery or in the event of a major gastrointestinal haemorrhage.

The durability of anticoagulation reversal is a concern with both the new anticoagulants and warfarin. For warfarin, laboratory coagulation monitoring is important following the use of reversal agents, as its long half-life (around 40 hours) may outlast the half-lives of the reversal agents.[4] The use of INR and associated threshold values requiring action are routinely used in monitoring of patients on warfarin.[5] However, it remains to be established which laboratory tests and what thresholds should be used to monitor patients treated with the new anticoagulants in the setting of bleeding requiring anticoagulation reversal. For dabigatran, the thrombin clotting time and the measurement of plasma dabigatran concentrations are expected to be particularly informative for clinical decision making.[6,7]

REFERENCES

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51. http://dx.doi.org/10.1056/NEJMoa0905561
2. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al.; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-52. http://dx.doi.org/10.1056/NEJMoa0906598
3. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, et al.; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014;129:764-72. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.004450
4. Chin PK, Doogue MP. Long-term prescribing of new oral anticoagulants. Aust Prescr 2016;39:200-4. http://dx.doi.org/10.18773/austprescr.2016.068
5. Tran HA, Chunilal SD, Harper PL, Tran H, Wood EM, Gallus AS; Australasian Society of Thrombosis and Haemostasis (ASTH). An update of consensus guidelines for warfarin reversal. Med J Aust 2013;198:198-9. http://dx.doi.org/10.5694/mja12.10614
6. Chin PK, Wright DF, Patterson DM, Doogue MP, Begg EJ. A proposal for dose-adjustment of dabigatran etexilate in atrial fibrillation guided by thrombin time. Br J Clin Pharmacol 2014;78:599-609. http://dx.doi.org/10.1111/bcp.12364
7. Glund S, Stangier J, van Ryn J, Schmohl M, Moschetti V, Haazen W, et al. Effect of age and renal function on idarucizumab pharmacokinetics and idarucizumab-mediated reversal of dabigatran anticoagulant activity in a randomized, double-blind, crossover phase Ib study. Clin Pharmacokinet 2017;56:41-54. http://dx.doi.org/10.1007/s40262-016-0417-0