Novel oral anticoagulants: too good to be true?

Michael Schachter

It is fair to say that the pharmacological therapy of cardiovascular disease has not been an area of spectacular growth in recent years. Little has happened in the treatment of hypertension and heart failure. There has been interest in the development of antiplatelet drugs in acute coronary syndromes and percutaneous interventions, but not in long-term cardiovascular prevention to compete with aspirin and clopidogrel. The one major area of intense interest has been the novel oral anticoagulants (NOACs), dabigatran, rivaroxaban and apixaban. The first of these is a direct thrombin inhibitor, while the other two are blockers of activated factor X. Two comprehensive reviews of these drugs are published in this issue of the Postgraduate Medical Journal.1–2 Despite their relatively high costs these drugs have been adopted widely in developed countries for the treatment of venous thromboembolic disease and especially for preventing stroke in atrial fibrillation. This represents a population of several hundred thousand in the UK alone and has been the greatest single driver for developments of the NOACs. The disadvantages of warfarin are well-known; the need for plasma level monitoring. As they respond between patients and, hence, no consensus has been that the new drugs are effective. As the two reviews indicate, the disadvantage of dosage based on plasma levels could reduce the risk of major haemorrhage by up to 40% as compared with well-controlled warfarin without any impact on the risk of ischaemic stroke. The incomplete nature of the evidence on which guidelines for this drug have been based was only disclosed in the course of litigation in the USA and by an investigation by the BMJ. Boehringer Ingelheim explained that such analyses were not shared with the regulators because the analyses did not provide a reliable prediction of patient outcomes, and the research did not support making dosage decisions based on plasma outcomes. Although regular monitoring of this drug would provide clear benefits to patients, it would also reduce any apparent advantage of the drug over warfarin, thus reducing this particular drug’s ‘selling point’. At the time of writing it is not clear what the regulatory consequence of these revelations might be. Are we likely to discover similar problems with rivaroxaban and apixaban? At the moment we do not know. But in view of their pharmacokinetic properties there may be grounds for cautious optimism. Dabigatran has multiple basic disadvantages: it has very poor bioavailability, 3–7%, even worse than the bisphosphonates; it is a prodrug which needs two steps to convert it into the active compound; and it is eliminated entirely through the kidneys. All these factors are almost guaranteed to maximise variability in individual pharmacokinetics, and they do not apply to the other drugs. They have bioavailabilities of 50–80% and are cleared by both liver and kidneys. But it would be reassuring to have all relevant analyses in the public domain.

Here is little doubt that the NOACs will have a significant role in anticoagulation—nearly, in stroke prevention in atrial fibrillation. But we are not yet confident that we can use them with maximal efficacy and especially maximal safety. It is not clear why dabigatran licensing was expedited in the USA. Everyone agrees that warfarin is far from ideal but it is effective and supported by decades of experience. This situation is hardly comparable to the treatment of cancers or infections where established treatments are ineffective and new treatments urgently need to be developed and tested. In the present situation, obligatory plasma level monitoring of dabigatran should surely be considered by the regulators and the manufacturer. But most disappointing, despite experiences of late withdrawals from use of drugs such as cerivastatin and rofecoxib,6–7 the complete disclosure of all relevant analyses does not always happen. It certainly should.

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