Initial experience with rivaroxaban in mechanical valve prosthesis in an animal model

José I. Aramendi* and Carlos A. Mestres

* Division of Cardiac Surgery, Cruces University Hospital, Barakaldo, Spain
b Department of Cardiovascular Surgery, Hospital Clínico, Barcelona, Spain

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Warfarin, first synthesized in 1940, and its derivatives like coumadin were the only available oral anticoagulant agents until recently. Even though it has immense efficacy as an anticoagulant, warfarin is universally acknowledged as a cumbersome agent to use. It has a delayed onset of action, unpredictable efficacy affected by genetics, race and ethnicity, co-administered drugs and diet, body weight and age of the patient [1]. It requires periodic monitoring to ensure therapeutic levels and despite careful follow-up, only ~50% of the patients are able to achieve therapeutic levels as defined by the international normalized ratio. In the last decade, new oral anticoagulants, like dabigatran and rivaroxaban have proved useful in preventing thromboembolic events in patients with non-valvular atrial fibrillation or in preventing deep vein thrombosis. They are administered orally at a fixed dose and do not require periodical blood test to assess efficacy. Recently, the preliminary results of the RE-ALIGN study have been published [2]. This Phase 2 dose-validation study evaluated the use of dabigatran in patients with mechanical heart valves. The study terminated prematurely because of an excess of thromboembolic and bleeding events. Authors concluded that the use of dabigatran in patients with mechanical heart valves showed no benefit and an excess risk.

Rivaroxaban, an oral factor Xa inhibitor, may provide more consistent and predictable anticoagulation than warfarin and eventually dabigatran. In the ROCKET AF trial [3], in patients with atrial fibrillation, rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

Pivotal clinical trials in the prophylaxis against venous thromboembolism (VTE) in orthopaedic patients following primary total hip and total knee arthroplasty have demonstrated the superior efficacy of rivaroxaban in reducing total VTE in comparison with standard regimens of enoxaparin. The safety of the drug was found to be excellent, with no demonstrable cardiovascular or hepatic effects and no statistically significant increase in major bleeding. A pooled analysis of data collected on the patients from the four RECORD trials revealed rivaroxaban to be the first antithrombotic agent to demonstrate superiority over another antithrombotic agent (enoxaparin) in reducing symptomatic VTE and all-cause mortality [4].

The most challenging indication for oral anticoagulation is the prevention of thrombosis after implantation of mechanical heart valve prosthesis. No human studies have been reported assessing the efficacy of rivaroxaban in preventing mechanical valve thrombosis. Greiten et al. [5] report in this issue of the Journal the use of rivaroxaban in an animal model implanted with mechanical bileaflet aortic valve prosthesis. They implanted a heterotopic valve conduit in 30 swine which were assigned to enoxaparin, rivaroxaban or no treatment (10 swine in each group). They measured valve thrombosis and platelet deposition. Rivaroxaban resulted superior to enoxaparin or no treatment in preventing thrombus or platelet deposition in mechanical valves, although a small amount of visible thrombosis was seen in 4 of 10 animals. The authors suggest that further investigations are required with a higher dose in order to safely evaluate the effects of rivaroxaban in this animal model. Noteworthy, safety of rivaroxaban was excellent with no evidence of haemorrhage or peripheral emboli on post-mortem examination.

This is the first short-term animal study of rivaroxaban in mechanical heart valves, and the authors should be congratulated. If fine-tuning of the appropriate dose can be achieved, the time has come for a Phase 3 trial in humans although some concerns have risen after the suboptimal results of the RE-ALIGN trial with dabigatran. As the authors state, ‘use of the drug would represent a major step forward in clinical care’ since it is a once-daily fixed dose, does not require blood test monitoring and safety does not seem to be an issue. As for its use in patients after aortic tissue valve replacement, there is growing evidence that antplatelet agents are efficacious in preventing thromboembolic episodes [6]. Rivaroxaban could be an attractive alternative in patients after aortic tissue valve replacement with associated atrial fibrillation if safety and efficacy are proven.

REFERENCES


