Peri-operative anticoagulant therapy – the case for an uninterrupted dose-adjusted warfarin regimen in the high-risk patient

It is generally held that the need for bridging therapy with heparin, when patients on long-term warfarin therapy interrupt their treatment during the peri-operative period, will depend on the patient’s risk of thrombo-embolism on the one hand and the risk of bleeding on the other. Although the optimal peri-operative anticoagulant management in patients with a mechanical prosthetic heart valve has not been determined on the basis of well-designed prospective randomised trials, several practical guidelines for clinicians have nevertheless been proposed. A refined approach is summarised briefly in Table I.

From these recommendations it would seem that despite the fact that warfarin therapy has been found to be highly effective in preventing systemic embolisation in high-risk patients with chronic atrial fibrillation or prosthetic heart valves, the prevailing view is to stop the warfarin and to switch to heparin during the peri-operative period. Therefore the concept of bridging therapy seems to imply that heparin is safer and more effective during the peri-operative phase when the risks of bleeding and thrombo-embolism are both concurrently raised. However, despite a thorough search of the literature, it would appear that reliable support for such a view is lacking.

In their classic article published in the Lancet in 1959, Sevitt and Gallagher from the Birmingham Accident Hospital reported that peri-operative full-dose anticoagulant prophylaxis with phenindione in middle-aged and elderly patients with fractures of the femoral neck proved to be effective and safe despite the peri-operative prothrombin activity (PA) values of 15 - 30% (with prothrombin times of 22 - 40 seconds or 2 - 3 times normal) using a saline extract of acetone-dried human brain as the source of thromboplastin. Whereas there were 2 cases of major bleeding among the 150 controls, there were 5 among the 150 in the phenindione series. Thrombo-embolism occurred in no patient in the treated group, but in the control series 18% developed embolism. In 10% of cases this was fatal. Hull et al. conducted a randomised double-blind study of 1 436 patients to evaluate the effectiveness and safety of low molecular weight heparin (LWMH) compared with warfarin to prevent venous thrombosis after hip and knee replacement. Their data demonstrated that the small reduction in the incidence of venous thrombo-embolism (VTE) with LMWH was offset by an increase in the bleeding complications.

Heparin failure

On the basis of several reports of heparin failure in pregnant patients with prosthetic heart valves, several authorities have expressed a preference for the use of warfarin in this particular patient group, despite the risk of warfarin embryopathy.

The case for the use of warfarin as an antithrombotic agent is further strengthened by the well-documented concept that clot-bound thrombin is an important mediator of thrombus growth. By reducing prothrombin levels and hence the

| TABLE I. PERI-OPERATIVE ANTICOAGULANT MANAGEMENT IN PATIENTS WITH A MECHANICAL PROSTHETIC HEART VALVE |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Thrombo-embolism risk category               | Patient’s characteristics                       | Suggested anticoagulant management           |
| High risk                                    | Recent (within 1 month) stroke or transient ischaemic attack, any mitral valve caged-ball* or single-leaflet tilting disc† aortic valve | Bridging anticoagulant therapy strongly recommended |
| Moderate risk                                | Bileaflet‡ tilting disc aortic valve and two or more stroke risk factors‡ | Bridging anticoagulant therapy should be considered |
| Low risk                                     | Bileaflet tilting disc aortic valve and fewer than two stroke risk factors§ | Bridging anticoagulant therapy is optional |

*Starr Edwards valve.
†Bjork Shiley, Medtronic-Hall or Omnicarbon valve.
‡St Jude or Carbomedics valve.
§Stroke risk factors: atrial fibrillation, previous stroke, transient ischaemic attack or systemic embolism, left ventricular dysfunction, age > 75 years, hypertension, diabetes mellitus.
amount of thrombin generated and bound to fibrin, oral anticoagulants contribute significantly to a decline in the thrombogenicity of existing thrombi with a consequent reduction in the prothrombotic state. Conversely, it would appear that clot-bound thrombin is protected from inhibition by the heparin-antithrombin complex. There is also the danger of a hypercoagulable rebound after the temporary cessation of warfarin.

A postoperative decline in plasma fibrinolytic activity is a well-documented finding. By inhibiting the postoperative rise in plasminogen-activator-inhibitor (PAI) levels, warfarin also curtails the fibrinolytic shutdown after operations. Sustained fibrinolysis may be an important mechanism for the protective actions of warfarin in the prophylaxis of thromboembolism after major surgery.

Despite the appeal for bridging therapy with heparin in the high risk-case, Verstraete and Wessler believe that it is safe to continue with the postoperative warfarin regimen throughout the surgical procedure, provided that the prothrombin time is not prolonged excessively. Uninterrupted warfarin therapy has also been suggested in oral, ophthalmic and hand surgery.

According to Sandset and Abildgaard of Oslo, clinical experience with peri-operative oral anticoagulants has shown that many types of surgery can be performed safely without an excessive risk of bleeding, provided that the international normalised ratio (INR) is less than 2.0 – an approach that is supported in several European countries. Even in abdominal surgery the Norwegian experience indicates that an INR of 1.5 - 1.8 does not increase the risk of peri-operative bleeding. The INR level will obviously depend on the type of surgery, for example in neurosurgery where bleeding may have serious consequences.

In a well-designed feasibility study of continuing dose-reduced warfarin for invasive procedures in 100 patients with high thrombo-embolic risk, Larson and colleagues from the University of Florida showed that moderate-intensity anticoagulant therapy with warfarin, targeting a goal INR of 1.5 - 2, appears to be a safe and feasible method for preventing thrombo-embolic complications in high-risk surgical patients receiving long-term anticoagulant therapy. With this regimen the warfarin dosage is halved 7 days before surgery, with a fine preoperative adjustment to an INR level of 1.5 - 2.

In view of these arguments concerning the use of heparin, uninterrupted dose-adjusted peri-operative warfarin therapy in the high-risk case with a prosthetic heart valve has also been our preference for a number of years. However, it should be underscored that in view of the well-known interactions between warfarin and several agents, such as non-steroidal anti-inflammatory drugs that increase the risk of warfarin-associated bleeding by inhibiting platelet function, a platelet count and template bleeding time in addition to a peri-operative thrombelastogram to assess global haemostatic integrity is of cardinal importance. This concept is strengthened by recent findings that despite similar INR values, there was considerable individual variation in platelet reactivity and that monitored platelet function would be of value to individualise oral anticoagulant regimens.

In view of the encouraging results of the Florida group as well as the extensive clinical experience in Norway and other centres, it would seem appropriate to submit the concept of continuing peri-operative dose-reduced warfarin for invasive procedures in patients with a high thromboembolic risk to the test of actuarial cross-examination based on a well-controlled randomised comparative clinical analysis.

R. C. Franz
Department of Surgery
University of Pretoria

REFERENCES