Warfarin Therapy in Acute Coronary Syndromes

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Plaque disruption, platelet activation and aggregation and thrombus formation are significant factors in the pathophysiology of acute coronary syndromes [1, 2]. Exposure of the subendothelial components following plaque rupture also activates the coagulation cascade, resulting in thrombin production (activation of platelets, factor V and factor VIII). Aspirin or clopidogrel, however, do not inhibit the platelet activation by thrombin. The addition of an antithrombotic drug (unfractionated heparin, low-molecular-weight heparin or direct antithrombin) has therefore been shown to be beneficial. The persistence and increased pro-coagulant activity up to 6 months following an ischaemic event [3] and the raised concentration of factor VII (associated with recurrent ischaemic events) [4] would favour the addition of an anticoagulant.

In this edition of *Heart Drug*, Askew et al. [5] have reviewed the evidence regarding the use of warfarin for both primary and secondary prevention in coronary artery disease and have described the possible mechanisms for its actions.

The Evidence

In primary prevention of ischaemic heart disease, although the combination of low-dose warfarin (INR 1.3–1.8) therapy with aspirin 75 mg improved efficacy compared to either therapy alone in high-risk men, this

resulted in increased fatal strokes and minor bleeding [6]. A follow-up study of the thrombosis prevention trial also suggested that warfarin may alter atheroma progression with a non-significant reduction in the incidence of angina compared to those treated with aspirin where an increased event rate was found. This study, however, was completed prior to the widespread use of cholesterol-lowering agents, and emerging clinical trial results would now support the combination of these drugs with aspirin in high-risk patients. The risk of bleeding will also be small.

The evidence regarding the use of warfarin and aspirin combination therapy in secondary prevention of ischaemic heart disease is convincing. The data, however, support the use of high-dose anticoagulation to achieve benefit. The Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis-2 study (INR 2.6) showed a 40% reduction in 3-month vessel reocclusion after successful fibrinolytic therapy [7], with significant improvement noted for clinical outcome [7, 8]. Significant benefits were also observed in the Warfarin Re-Infarction Study-2 trial over a follow-up of 4 years (INR 2.2; primary end point of death, reinfarction and stroke: 15% with combination therapy versus 20% with aspirin alone) [9]. Compliance with medication and accurate anticoagulation management, however, are important to achieve benefit, as shown by the Organization to Assess Strategies for Ischemic Syndromes-2 trial, where no benefit was observed in the overall study results (7.6% with combination therapy versus 8.3% with aspirin, $p = 0.4$),

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but significant benefit was observed for compliers (good compliers, primary end point: 6.1% with combination therapy versus 8.9% with aspirin alone, $p = 0.02$) [10].

Clinical Considerations

The data thus far provide support for the use of oral anticoagulation in combination with aspirin, especially for secondary prevention in ischaemic heart disease. The time required to achieve adequate anticoagulation with warfarin varies between patients and can be prolonged, and in view of the rise in thrombotic risk during commencement of treatment, patients will require the addition of heparin initially. In view of the potential risks of haemorrhage, appropriate patient selection is paramount. Patients with a history of falls, gastrointestinal haemorrhage, hypertension, renal impairment, anaemia, older age, stroke and bleeding diathesis are at increased risk. Regular anticoagulation checks, preferably by a dedicated team, will ensure and improve target INR and compliance. The use of patient self-check INR kits and warfarin dose adjustments at home by selected patients should be of benefit.

The use of warfarin in female patients is less clear, especially for primary prevention. Furthermore, the embryonic and teratogenic risks associated with warfarin therapy require careful consideration in young females. If anticoagulation is indicated in patients who are pregnant, heparin should be used.

The difficulties that exist with warfarin anticoagulation may reduce patient compliance and adherence to therapy. The length of treatment is also not established. The combination of aspirin and clopidogrel, for which significant benefits have been shown in patients with ischaemic heart disease without the need for monitoring, has been advocated [11], but no study has compared the clopidogrel and aspirin combination with that of aspirin and warfarin therapy, or the combination of all three agents in primary or secondary prevention of ischaemic heart disease.

Recommendations

Appropriate selection of suitable patients with minimal risk of haemorrhage is important. Careful management of anticoagulation, preferably by a dedicated team, would improve compliance and maintenance of therapeutic INR. The use of warfarin as monotherapy in the setting of ischaemic heart disease and atrial fibrillation (primary or secondary prevention) is established, especially if the arrhythmia is persistent or recurrent. Other clinical scenarios include patients who are diagnosed with post-myocardial infarction left ventricular thrombus, left ventricular aneurysm and severe left ventricular dysfunction. Oral anticoagulation should also be considered in those who are intolerant of aspirin or clopidogrel.

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