Drugs 2001; 61 (4): 523-524
0012-6667/01/0004-0523/$27.50/0

Argatroban

A Viewpoint by Jeanine M. Walenga

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Argatroban was discovered in the 1970s by S. Okamoto in Japan. It was first clinically used in patients for treatment of peripheral arterial occlusive disease in the early 1980s. In Japan today argatroban is approved for treatment of arterial thrombosis (approved 1990), acute cerebral thrombosis (1996) and anticoagulation of antithrombin (AT) III deficient patients undergoing haemodialysis (1996). In 2000 argatroban was approved in the US for prophylaxis and treatment of thrombosis associated with heparin-induced thrombocytopenia (HIT) type II. These clinical trials have proven argatroban to be a safe and effective treatment of thrombosis. The submission to the European health authorities for use of argatroban in patients with HIT is in progress.

Argatroban offers several advantages over traditional anticoagulants. In comparison with heparin argatroban is a selective, direct inhibitor of thrombin that is not dependent on ATIII or other cofactors. Its anticoagulant properties are more potent than those of heparin or low molecular weight heparins for bound thrombin, and the mechanism of action of argatroban is less complex than that of warfarin.

Aside from argatroban 2 other thrombin inhibitors, hirudin and bivalirudin (hirulog), have recently been approved in the US. These drugs are pharmacologically distinct from argatroban and exhibit different tolerability/efficacy profiles. Thus, the clinical actions of one may not be the same as the other. Argatroban has a rapid onset of action and is rapidly reversed following discontinuation. This characteristic provides a wider safety net than that of the irreversible inhibitors hirudin and bivalirudin. Argatroban is not a protein as is hirudin, and thus it should not generate antibodies that increase its anticoagulant activity by prolonging its elimination half-life, nor should it produce antibodies that decrease its anticoagulant effect by neutralising the drug. Because it is of similar structure to hirudin, bivalirudin may also generate antibodies. Argatroban is cleared through the liver not the kidney as hirudin is, and thus it can be used in patients with renal disease without dosage adjustment. The thrombin inhibitors have varying effects on the traditional activated partial thromboplastin time (aPTT). Because argatroban has a very good dose-dependent effect on the aPTT, this assay can easily be used for dose adjustment minimising the bleeding risk.

Current clinical trials of argatroban focus on its use in disseminated intravascular coagulation, thrombolysis, coronary artery thrombosis, percutaneous coronary intervention and thrombotic stroke. Studies on drug interactions are lacking.

The introduction of thrombin inhibitor drugs, such as argatroban, has added a new dimension to the management of thrombosis. These drugs offer a unique substitute for anticoagulation in patients that are heparin compromised, a position we have not had prior to now. Argatroban appears to be a safe drug, with an uncomplicated dosage regimen and consistent response between individuals. With an increased awareness of heparin-associated thrombosis and the litigation that can accompany this, the use of thrombin inhibitors may become widespread. ▲