

An Update on Argatroban Anticoagulant Therapy

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The parenteral thrombin inhibitors are now known to play an important role in the antithrombotic management of heparin compromised patients. In particular, these drugs are of crucial importance for patients with heparin-induced thrombocytopenia (HIT) requiring anticoagulation. Currently, such direct thrombin inhibitors as recombinant hirudin, angiomas and argatroban are available in the US. In Europe, only hirudin is available for this indication and argatroban is under consideration by the regulatory agencies. Argatroban represents a synthetic direct thrombin inhibitor (DTI) which has been used in various clinical indications in Japan for nearly 15 years. Long before the development of hirudin and angiomas. Thus, argatroban represents the very first antithrombin agent used clinically in such indications as management of chronic arterial occlusion, acute cerebral thrombosis and for thrombophilic patients undergoing hemodialysis. The US FDA has also approved this agent in the anticoagulant management of HIT patients undergoing percutaneous intervention. Unlike other DTIs which are approved for clinical use, argatroban is a peptidomimetic (arginomimetic) drug with reversible mechanisms of inhibition of thrombin. The available pharmacological data on this drug, along with some of the clinical observations on its vascular effects, cannot be simply explained on the basis of its inhibitory actions on thrombin. Besides a direct inhibition of thrombin, this drug is also found to inhibit thrombogenesis in various assay systems indicating inhibitory actions on other enzymes involved in the coagulation cascade. Studies carried out using proteomics suggest that tissue factor-VIIa mediated conversion of factor X to factor Xa is also blocked by this agent. In clinical samples obtained from therapeutic ($\sim 1.0 \mu\text{g/ml}$) and interventional ($\sim 2.5 \mu\text{g/ml}$) studies, argatroban also down-regulated the functional thrombin activatable fibrinolytic inhibitor (TAFI) thereby facilitating fibrinolysis. At therapeutic levels, argatroban enhanced the tissue factor pathway inhibitor mediated inhibition of factor Xa and the generation of factor VIIa. In the thrombin generation assays FPA, TAT and F1.2, argatroban was found to produce strong inhibition in a concentration dependent fashion. Argatroban produced strong anticoagulant effects in whole blood as measured by the activated clotting assay. At concentrations of 2-5 $\mu\text{g/ml}$ it produced anticoagulation comparable to heparin by producing ACT levels of 250-350 seconds. Using flow cytometric methods it was clearly demonstrated that argatroban produced a strong inhibition of tissue factor mediated activation of platelets. Initial studies have indicated that argatroban also impaired the oxidative burst process in leucocytes. In cultured endothelial cells, this agent produced an up-regulation of nitric oxide (NO), an observation which was also reported for patients plasma upon evaluation of various endothelial markers. Pretreatment with argatroban also reduced the contractile response of the normal human serum induced response of rat aortic strips. In these animals NO levels were also increased. Unlike both hirudin and bivalirudin, argatroban did not induce any antibodies in plasma obtained from patients treated with this agent. The anticoagulant responses to argatroban of hirudin and bivalirudin treated patients with respective antibodies were not modified, suggesting that argatroban does not

have any cross reactivity with these antibodies. At equivalent anticoagulant levels comparable to hirudin and bivalirudin, argatroban did not compromise the activation of protein C by thrombomodulin complex. More recently, argatroban has been found to produce down regulation of such inflammatory cytokines as CRP, CD 40 ligand and MCP-1. These studies clearly suggest that argatroban, besides being a strong thrombin inhibitor, produces its effects also by targeting platelets, white cells and endothelial cells. This presentation will provide a detailed account of the mechanisms of argatroban actions with particular reference to its clinical effects in the anticoagulant management of HIT type II and anticoagulation in percutaneous intervention. Furthermore, an update on the recently completed clinical; trials on HIT, interventional cardiology and drug interactions will be provided. The relative merits of argatroban as a parenteral anticoagulant for potential hematologic indications such as its potential use in stem cell transplantation, sickle cell crisis and malignancy associated thrombosis will also be highlighted.

References

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