Argatroban (Novastan) Protocol  
Ver 1.3.903

Argatroban is a synthetic direct thrombin inhibitor that may be chosen as an alternate anticoagulant for patients that are heparin-intolerant, including those with congenital and acquired ATIII deficiencies, those with heparin-induced thrombocytopenia (HIT) and those with high levels of polymorphonuclear granulocyte elastase. Because argatroban has a fast acting anticoagulant effect without any cofactors such as ATIII, this drug is a favorable anticoagulant for heparin-intolerant patients with antithrombin III deficiencies requiring extracorporeal circulation. In adverse reactions to heparin, heparin acts as an antigen after complexing with platelet factor 4, which leads to life-threatening heparin-induced thrombocytopenia. As argatroban prevents heparin-induced platelet aggregation, it is effective for use as a therapeutic anticoagulant. [Matsuo, 1997 #10] 

Argatroban is capable of inhibiting the action of both free and clot-associated thrombin. It is metabolized by the liver with terminal elimination half-life of argatroban approximately 39 to 51 minutes.

Test Used to Identify HIT II

- Platelet C serotinin release assay: 94% sensitivity with specificity of 100%, test is difficult, time-consuming, and requires radioactive isotopes.
- Heparin-induced platelet aggregation assay (HIPAA): 90% sensitivity with specificity of 100%, measures platelet aggregation optically. Utilization of a hapariniod (Orgaran (danaparoid)) to detect cross reactivity.
- Heparin-PF4 enzyme linked immunosorbent assay (PF 4 ELISA): immulonological test that depends on the direct detection of heparin-induced antibodies.
- Lumiaggregometry: platelet aggregation with simultaneous measurement of ATP release.
- Flow cytometric assays

How to Monitor Argatroban

- Activated clotting time values and the effect of argatroban during cardiopulmonary bypass have indicated a dose dependent response correlation. [Sakai, 1999 #11].
- When administered as a bolus dose, argatroban produced dose-related increases using an activated clotting time (ACT) and activated partial thromboplastin time (aPTTT) within 10 minutes of administration. 
- Any suitable ACT machine can be utilized to monitor the anticoagulant state.
- The target ACT range for PCI procedures is >300 sec and <450 sec. Target ACT range for CPB is >400 sec.
- Dissipation of anticoagulant effect was approximately 4-fold faster for argatroban than for heparin.
Dosing Regimen (Per manufacturer recommendation)

- Start infusion at 25 ug/kg/min and a of 350 ug/kg administered over 3-5 minutes – no argatroban is added to the pump (SLMC typically keeps 4 vials on hand).
- ACT should be checked 5-10 minutes after the bolus dose is completed.
- Therapeutic ACT values are usually attained with 10-15 minutes after initiating the bolus.
- Dosage adjustment may be required if ACT <400 seconds or >450 seconds
  - If ACT < 300
    - An additional dose of 150 ug/kg should be given; increase infusion dose to 30 ug/kg/min.
  - If ACT > 450
    - Decrease infusion dose to 15 ug/kg/min.
- While on CPB, the drug infusion will take place through the heart-lung machine and be diligently monitored by the perfusionist.

Cardioplegia Delivery

An intermittent blood-based cardioplegia system is contraindicated due to the rapid dissipation of the anticoagulant effect.¹ If blood-based cardioplegia is utilized, it must be continuous or be continuously recirculated in between delivery doses. It is recommended to use crystalloid cardioplegia – cold induction and cold maintenance with Dr. Seifert’s cardioplegia, with a maintenance dose every 20 minutes.

Circuit Monitoring

- Heparin coated circuits are contraindicated. This includes the use of the CDI heparin bonded in-line blood gas monitor components.
- Suggestion - The pre and post oxygenator pressures should be measured to give the perfusionist a better picture of the integrity of the oxygenator.
- Test verification of appropriate anticoagulation will be monitored every 20 minutes.

Things to Remember

- Argatroban, due to its small molecular size, can be removed with the hemoconcentrator; therefore, hemoconcentration should be avoided if possible.
- There is no reversal agent for argatroban.
- Half-life of argatroban is roughly 15 minutes (unaffected by dose)². Latest manufacturer information states a half-life between 39-51 mins.
- Once you have terminated bypass re-circulate circuit and send circuit volume to the cell saver as soon as possible (when A line is out). It is advisable to flush your entire circuit through with Plasmalyte to maintain a viable circuit.
- Heparin cannot be used with the cell saver – CPD or citrate could be used as the substitute for heparin.
- No dosage adjustment is necessary in patients with renal dysfunction; however, the dosage of argatroban should be decreased in patients with hepatic impairment. (package insert)
- Deep hypothermia circulatory arrest (DHCA) is currently contraindicated.

References