Strategies for Reversal of Anticoagulants, Part 2: The Newer Anticoagulant Agents  
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INTRODUCTION
In the last decade, several new anticoagulants have been developed for prevention and treatment of thromboembolism and for treatment of patients with heparin induced thrombocytopenia (HIT). In Part 2 of this review, we will summarize some of the newer anticoagulant medications and strategies for their reversal.

DIRECT THROMBIN INHIBITORS
Direct Thrombin Inhibitors (DTI’s) inhibit thrombin by directly binding to the exosite and/or active site of thrombin. They have a short half-life and are administered by continuous IV infusion.

Indications: Treatment of patients with HIT or those with a history of HIT undergoing cardiac surgery or percutaneous coronary angioplasty.

There are currently three DTI’s approved by the US FDA: lepirudin, argatroban and bivalirudin.

Antidotes: No specific antidotes are available for any DTI’s, which may pose a serious risk for bleeding.

BIVALIRUDIN
Bivalirudin is a semi-synthetic polypeptide in the hirudin family of anticoagulants. It interacts with both the active site and exosite of thrombin, resulting in irreversible bivalirudin:thrombin complexes.

Elimination: Proteolysis 80% and renal 20%. Bivalirudin is partly removed by hemodialysis and ultrafiltration: Hemodialysis- 25%, hemofiltration 43-65%, plasmapheresis- 69%.

Half-life: approximately 20-25 minutes in patients with normal renal function. Half-life can be increased up to 3.5 hours in patients with severe renal impairment, but ranges from 10 minutes to 210 minutes.

The theoretical advantage of bivalirudin over other DTI’s is a short half-life and drug removal with hemofiltration.

Dose: For treatment of HIT, 0.15-0.2 mg/kg/h (in patients with normal renal function). In patients with impaired renal function, an average dose of 0.03-0.05 mg/kg/h has been used. There is no need for dose adjustment in patients with hepatic insufficiency.

Monitoring: Adjust the dose to maintain aPTT values 1.5-2.5 times the patient’s baseline. Supratherapeutic aPTT values (>2.5 times the patient’s baseline) are most common during initiation of treatment, especially in patients with impaired renal function. The aPTT has been shown to correlate with plasma levels of bivalirudin at all levels of renal function.

LEPIRUDIN
Lepirudin is also a member of the hirudin family of anticoagulants and interacts with both the active site and exosite of thrombin, resulting in irreversible lepirudin:thrombin complexes.

Elimination: Renal

Half-life: Approximately 60-90 minutes. It has the longest half-life of all DTI’s.

Dose: For HIT treatment, a 0.4 mg/kg bolus, followed by an infusion of 0.15 mg/kg/h. Dose adjustment is required for patients with impaired renal function.

Formation of antihirudin antibodies has been observed in up to 40% of patients treated with lepirudin for more than five days.

Monitoring: The infusion is adjusted to prolong the aPTT to values 1.5-2.5 times the patient’s baseline. Some places use the Esparin clotting time (ECT) for monitoring lepirudin; however ECT is not readily available in most laboratories. There is a debate regarding the best method for monitoring lepirudin, since at higher plasma hirudin levels, the correlation between aPTT and hirudin is not linear.

ARGATROBAN
Argatroban binds reversibly to thrombin’s active site.
Elimination: Hepatic

Half-life: 40-50 minutes. Prolonged clearance can be seen in critically ill patients and in patients with impaired hepatic function. Antibody formation has not been reported with argatroban.

Dose: For HIT treatment in patients with normal liver function, 2 mcg/kg/min. For patients with moderate hepatic impairment, the dose can be reduced to 0.5 mcg/kg/min. Steady-state plasma concentration is reached within 1-3 hours.

Monitoring: The infusion is adjusted to prolong the aPTT to values to 1.5-2.5 times the patient's baseline. The aPTT has been shown to correlate well with plasma levels of argatroban.

**MANAGEMENT OF OVERANTICOAGULATION/BLEEDING ASSOCIATED WITH DTIs:**

Significant bleeding is especially common during the initial titration period prior to achievement of therapeutic levels. The rate of bleeding with DTI's is 5-20%. All DTI's have an effect on the INR: lepirudin has the least effect, followed by bivalirudin, then argatroban.

Methods that can be used to control life-threatening, non-surgical bleeding associated with DTI's include:

1) Modified ultrafiltration and hemodialysis which may facilitate removal of bivalirudin. Modified ultrafiltration is not available at every institution, but can eliminate 45 to 69% of bivalirudin, depending on the filter type. The elimination of lepirudin or argatroban is less effective or unclear. Hemodialysis decreases the plasma concentration of bivalirudin by only 25%. Neither lepirudin nor argatroban are eliminated by dialysis.

2) Recombinant activated factor VII (rFVIIa) has been used at a dose of 90 mcg/kg IV. A second dose can be given if bleeding continues; success has been marginal.

3) Blood products can be used to provide coagulation factors. Additionally, fibrinogen in the form of fresh frozen plasma or cryoprecipitate can be given to work as a competitor to displace bivalirudin from thrombin.

4) Antifibrinolytic drugs such as Amicar can be used.

**FONDAPARINUX (ARIXTRA)**

Fondaparinux (Arixtra) it is a synthetic pentasaccharide that works as a selective factor Xa inhibitor.

Elimination: Renal – contraindicated in patients with creatinine clearance < 30 mL/min.