

CHAPTER 18

Anti Thrombotic Agents

Direct Thrombin Inhibitors (DTI)

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In contrast to UFH and LMWH, direct thrombin inhibitors (DTI) are able to inhibit thrombin directly without the need for the cofactor antithrombin and to inhibit both fibrin-bound and soluble thrombin.

Rationale of Direct Thrombin Inhibitors in CAD

Direct thrombin inhibitors were developed to overcome the inability of the heparin/antithrombin complex to inactivate bound thrombin and to overcome the following problems with thrombolytic therapy in ACS, which necessitate more prolonged anticoagulation treatment:

1. Thrombus material remains at the coronary lesion for several months after an acute MI.
2. The coagulation system remains activated for 3-6 months after an acute event.
3. When anticoagulant treatment with indirect thrombin inhibitors is stopped, patients often experience re-activation of the coagulation system and rebound ischemic events.

When bound to fibrin, fibrin degradation products, or subendothelial matrix, thrombin is resistant to inactivation by the heparin/antithrombin complex. Bound thrombin, which remains enzymatically active, triggers thrombus growth by activating factors V, VII and XII, thereby amplifying thrombin generation. Bound thrombin also activates platelets.

Classification of Direct Thrombin Inhibitors (DTI)

A. Parenteral

1. Hirudin (Lepirudin).
2. Bivalirudin (Hirulog).
3. Argatroban.

B. Oral

- Ximelagatran.

Potential Advantages of Direct Thrombin Inhibitors over Heparin

- No binding to plasma protein. This results in a predictable anticoagulant response.
- Not neutralized by platelet factor 4. A maintained anticoagulant activity in the vicinity of platelet-rich thrombi can be achieved.
- Inhibition of fibrin-bound thrombin as well as fluid-phase thrombin. This results in a greater attenuation of thrombus growth.
- Because of their relatively small size, the interaction of the DTIs with the active site of thrombin is not compromised following binding of thrombin to fibrin at exosite 1.
- Low molecular-weight DTIs such as bivalirudin and argatroban, are better able to inhibit thrombin bound to fibrin clots than hirudin.

Table (18-1): Comparison of the Properties of Hirudin, Bivalirudin, and Argatroban

	Hirudin	Bivalirudin	Argatroban
Molecular mass	7000	1980	527
Site(s) of interaction with thrombin	Active site and exosite 1	Active site and exosite 1	Active site
Renal clearance	Yes	No	No
Hepatic metabolism	No	No	Yes
Plasma half-life, min	60	25	45

Source: Circulation 2002. Weitz and Buller

INDICATIONS AND CLINICAL USE OF DTI

Bivalirudin

- Currently, bivalirudin is the only DTI with an established indication in ACSs.
- When bivalirudin was administered before streptokinase, TIMI-3 flow was achieved in 85% of patients after 90 minutes.
- Bivalirudin is safer and more effective than heparin in patients undergoing PCI for post-infarction angina.
- By better inhibiting thrombin-mediated platelet aggregation, bivalirudin may diminish the need for additional therapy.
- Bivalirudin is the only agent licensed for use in patients with a history of heparin-induced thrombocytopenia.
- Bivalirudin produces more bleeding in AMI (table 18-2) than heparin when used in conjunction with streptokinase (HERO 2 trial 2001), otherwise bivalirudin is safer than heparin for all other clinical indications.

Administration

- Bivalirudin is given as an intravenous bolus followed by a 4-hour infusion during PCI.
- When used for treatment of patients with established heparin-induced thrombocytopenia and thrombosis, bivalirudin is given by continuous intravenous infusion until the platelet count rises, at which time warfarin therapy can be initiated.
- Dosages regimens:
 - Low-dose: 0.125 mg/kg IV bolus, followed by infusion at 0.25 mg/kg/h for 12 hours, followed by an infusion at 0.125 mg/kg/h for <60 h.
 - High-dose: use double the previous dosages.
 - Bivalirudin needs careful monitoring when used as an adjunct to thrombolytic therapy.

Table (18-2):Results of HERO 2 Trial: AMI. SK+Bivalirudin vs Heparin

	Bivalirudin (n=8516)	Heparin (n=8557)	<i>P</i>
30-day mortality (%)	10.8	10.9	0.876
30-day death +MI (%)	12.9	14.2	0.023
30-day reinfarction (%)	3.5	4.5	0.001
Intracranial hemorrhage (%)	0.55	0.37	0.09
Severe hemorrhage (%)	0.7	0.5	0.08

Source: XXIII Congress of the ESC 2001

Hirudin

- Hirudin appears to be superior to heparin in patients with unstable angina.
- In patients with unstable angina, hirudin and GP IIb/IIIa antagonists produce similar reductions in the risks of recurrent ischemia.
- Hirudin did not show any significant benefit over heparin in ACS in terms of mortality or reinfarction.
- Hirudin reduced the rate of reinfarction by 14% in patients with ST elevation, but it had no advantage over heparin in reducing mortality after 30 days.
- Like heparin, hirudin is not able to inhibit clot-bound thrombin.
- Rates of major bleeding are higher with hirudin than with heparin when given as adjunct to thrombolytic therapy.
- The relative increase in bleeding with hirudin compared with heparin, is similar to that produced by addition of a GP IIb/IIIa antagonist to heparin.
- Hirudin produces a greater reduction in death or MI than heparin in patients undergoing PCI.
- Hirudin is cleared via the kidney and should not be used in patients with impaired renal function.

Argatroban

- It is an active site-directed thrombin inhibitor and it has the smallest molecular mass.
- Initial trials did not show superiority over heparin.
- Argatroban and other active site-directed thrombin inhibitors (efegatran and inogatran) are undergoing clinical trials.

Limitations of Parenteral DTI

1. Cost: DTI particularly hirudin are considerably more expensive than heparin.
2. No specific antidote for overdosage.
3. Inability to block thrombin generation. The early beneficial effect is lost after discontinuation of therapy.

ORAL DIRECT THROMBIN INHIBITORS

Ximelagatran

Actions

- Ximelagatran is a direct thrombin inhibitor, administered as an oral prodrug, that is rapidly absorbed and bioconverted to the active form, melagatran .
- Melagatran provides rapid, direct, competitive, potent, selective and reversible inhibition of thrombin.
- Melagatran inhibits both free and clot-bound thrombin and inhibits thrombin-induced platelet activation and aggregation.
- Melagatran has a profibrinolytic effect, increasing the levels of fibrin degradation products.
- Melagatran inhibits the formation of both venous (fibrin-rich) and arterial (platelet-rich) thrombi

Pharmacokinetics

- Onset of action is almost immediate.
- Ximelagatran shows rapid oral absorption and bioconversion to active melagatran.
- Melagatran elimination is mainly by renal excretion.
- Unlike warfarin, melagatran and Ximelagatran do not interact with food, alcohol, or the major enzymes of the CYP 450 system, with low potential for drug-drug interaction.
- No dose adjustment is needed for age, obesity or ethnic origin.
- Half-life after oral dosing in healthy volunteers is 3 hours and in patients is 4-5 hours.
- The offset of action of melagatran is rapid following discontinuation of oral Ximelagatran, with low but pharmacologically active concentrations of melagatran remaining for approximately 12-24 hours after dosing.

Indications

1. Coronary artery disease: following AMI.
2. Atrial fibrillation.
3. Prophylaxis against thromboembolism.

Use of Ximelagatran in Coronary Disease

- Ximelagatran was significantly more effective than placebo in reducing death, non-fatal reinfarction and severe recurrent ischemia among patients following AMI.
- The reduced risk was observed within the first month and the difference was maintained, or even increased, over the six months of treatment (ESTEEM trial).

- The relative risk reduction by ximelagatran is of a similar magnitude to that observed in trials of well-controlled warfarin or clopidogrel in combination with aspirin in patients with MI.
- Ximelagatran was effective in patients with recent MI (both ST elevation and non ST elevation).

Safety

- Incidence of major bleeding (fall in hemoglobin of at least 20 g/L) is not significantly increased.
- Transient increase in liver enzymes (greater than three times the upper limit of normal) is detected after 2-6 months of treatment in 6.5-13% of patients. These elevations are transient and asymptomatic.

Use of Ximelagatran in Atrial Fibrillation

- Because of its immediate antithrombotic effect, ximelagatran has the potential to be an oral replacement for not only warfarin but also heparin.
- When compared with warfarin in patients with non valvular AF and at least one additional risk factor for stroke (SPORTIF III trial), ximelagatran showed a significant reduction in events (stroke, or a systemic embolic event) and a trend toward lower event rate.

Dosage

- One tablet 24 mg is given twice daily.

Contraindications

- Severe renal impairment (CrCl <30 ml/min).
- Clinically significant active bleeding.
- Hepatic impairment or a pre-treatment liver enzyme (ALT) value >2 times upper limit of normal.
- Known hypersensitivity to ximelagatran.

XIMELAGATRAN

- Oral direct thrombin inhibitor
- Immediate antithrombotic effect
- Oral replacement for warfarin and heparin
- Easier and potentially safer to use
- SPORTIF III trial in nonvalvular AF : significant reduction of stroke and systemic embolism (AHA-Chicago 2003, JACC 2003)
- ESTEEM trial for secondary prevention after MI : combination with ASA is more effective than ASA alone in preventing CV events (ESC- Vienna 2003, Lancet 2003)

NOVEL ANTITHROMBOTICS

Factor Xa inhibitors

Fondaparinux

- A synthetic pentasaccharide with nearly complete bioavailability after subcutaneous injection.
- Compared with LMWH, Fondaparinux reduces the incidence of asymptomatic venous thromboembolism in orthopedic surgery by approximately 50%.
- It is as effective and safe as LMWH and UFH in the treatment of deep venous thrombosis and pulmonary embolism.
- It is under trial in patients with ACS. Once-daily subcutaneous injections of Fondaparinux have similar efficacy and safety to UFH and LMWH.