

# CHAPTER 17

## Antithrombotic Agents

### *Heparins*

- Structure
- Mechanism of Action
- Pharmacokinetics
- Limitations of Unfractionated Heparin
- Heparin Induced Thrombocytopenia
- Heparin Rebound
- Low Molecular Weight Heparins
- Therapeutic Applications of Heparin

## HEPARIN

### Structure

Heparin is a heterogenous mucopolysaccharide made of alternating units of D-glucosamine and uronic acid.

### MECHANISM OF ACTION

#### Molecular Mechanisms

- Thrombin molecule has three binding sites (figure 17-1)
  1. Exosite 1: which is the substrate binding site. Thrombin binds to fibrin via exosite 1, it uses exosite 1 to dock on its substrate.
  2. Exosite 2: which is heparin binding site.
  3. Active site: which is the catalytic site that lies within a narrow cleft on molecule's surface.
- Heparin derives the majority of its anticoagulant activity from its interaction with antithrombin (an endogenous thrombin inhibitor made in liver).
- To inactivate thrombin, the heparin molecule must bind to both antithrombin (AT) and thrombin, forming a ternary complex. AT is an  $\alpha$ -globulin occurring naturally in the body.
- A chain length of at least 18 saccharide is necessary to form a ternary complex of heparin, antithrombin and thrombin (figure 17-1).
- By inducing a conformational change in antithrombin (AT), heparin accelerates its ability to inactivate thrombin a thousand fold, bringing thrombin in close proximity to AT.
- The heparin-AT complex binds avidly and reversibly to the active site of activated factors Xa, XIIa, XIa, and IXa and protein C.

Factor Xa inhibition is one-tenth that of thrombin inhibition.
- Heparin can mediate tissue factor pathway inhibitor (TFPI) mobilization which is another mean to limit thrombosis.
- Heparin molecules that contain fewer than 18 saccharide units i.e. low- molecular-weight heparins (LMWHs) are unable to bind thrombin and AT simultaneously and are unable to form ternary complexes to accelerate thrombin inhibition, but can inhibit factor Xa.
- Heparin is largely ineffective against fibrin bound or clot bound thrombin and against factor Xa bound in the prothrombinase complex and to the soluble fibrin degradation products.
- Like thrombin, factor X is also inhibited indirectly by heparin through the binding of AT (figure 17-1). Unlike thrombin, factor X does not require heparin binding for inactivation (i.e. ternary complex formation).
- LMWHs demonstrate less inhibitory activity against the thrombin than against factor X, because only 25% to 50% of the LMWH chains are long enough to bridge AT to thrombin.

- At lower concentrations, heparin molecules are unable to inhibit clot-or fibrin-bound thrombin molecules, because the heparin binding site may be less accessible when these thrombin complexes occur. This clot bound thrombin is still enzymatically active.

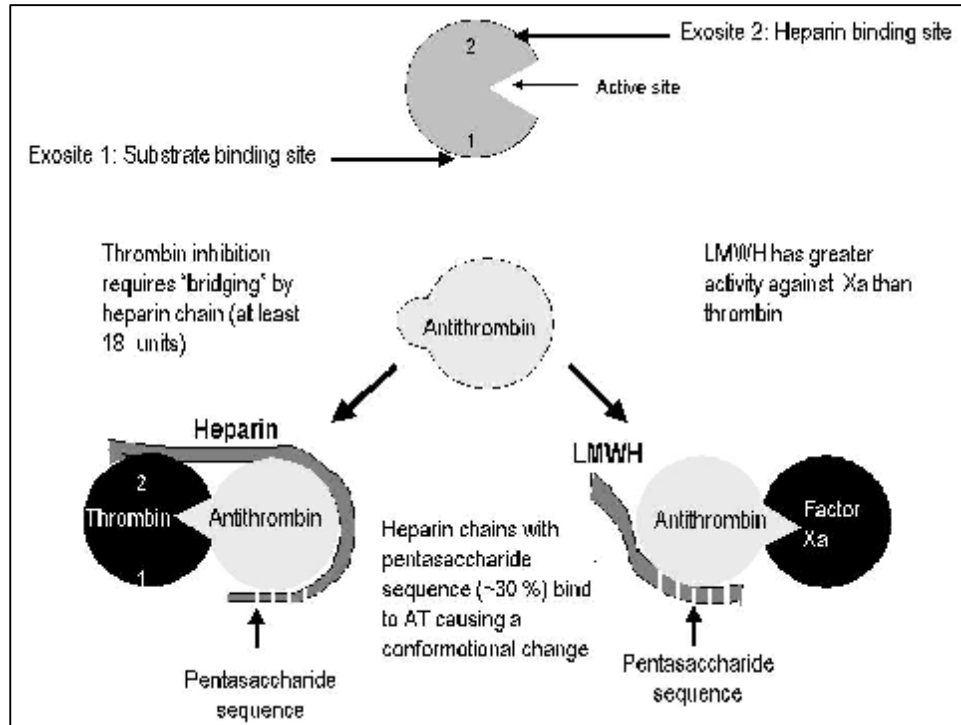


Figure (17-1): Antithrombotics- Heparin

Source: J Invasive Cardiol; 14:8B-18B,2002 [Suppl B]

### Pharmacokinetics

- Heparin can be administered both intravenously and subcutaneously.
- After subcutaneous injection, the anticoagulant effect is delayed for 1-2 hours, with peak levels at approximately 3 hours.
- High doses must be administered to compensate for reduced bioavailability.
- Bioavailability of heparin is markedly enhanced by intravenous infusion, and an intravenous bolus is required for an immediate anticoagulant effect.
- The half-life of heparin varies depending on the dose given, but is approximately 60-90 min.
- Heparin is cleared through renal elimination and through binding to receptors on endothelial cells and macrophages.
- Anticoagulant action of heparin is not linear, both intensity and duration of anticoagulant effect increase with increasing doses.

### Limitations of Unfractionated Heparins

- Non specific binding to plasma proteins and endothelial cells, which inactivates heparin.  
This results in variability in anticoagulant effect.
- Release of platelet factor 4 and von Willibrand factor from platelets which results in heparin resistance and a need for higher levels of heparin.
- Inability to inactivate fibrin-bound thrombin.  
Thrombin remains active when bound to fibrin.
- Heparin induces platelet activation.
- Formation of heparin antibodies. This can result in heparin-induced thrombocytopenia and thrombosis syndrome.
- Non linear increase in half-life as dose increases.
- Heparin rebound

### Heparin-Induced Thrombocytopenia (HIT) and Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS)

- HIT may occur following the formation of platelet antibodies as a consequence of heparin therapy. It is characterized by a reduction in the number of platelets approximately 6 to 10 days after the initiation of therapy, necessitating the immediate discontinuation of heparin.
- HITTS is characterized by decreased number of circulating platelets and thrombosis within the vasculature.
- Diagnosis of HIT and HITTS
  - Decrease in platelet count  $\geq$  30% from baseline.
  - Platelet count below lower limit normal range (<150,000).
  - Unexplained new arterial or venous thrombosis.
  - Unexplained disseminated intravascular coagulation.
- Management of HITTS
  1. Stop heparin.
  2. Manage thrombo embolism.
    - Medical: - Anticoagulation.
      - Warfarin, Dextran 40, LMWH
      - Antithrombins: Hirudin, Hirulog, Argatroban
      - Thrombolytic therapy.
    - Surgical: - Arteriotomy and clot extraction.
      - Fogarty catheter extraction of clot.
  3. Antiplatelet agents
    - Aspirin, clopidogrel, iloprost

4. Manage immune process
  - Plasmapheresis
  - IV gammaglobulin

#### Heparin Rebound

- The precipitation of thrombotic coronary arterial events after unfractionated heparin cessation has been termed "heparin rebound".
- Recurrence of symptoms and the development of thrombotic events after the cessation of heparin.
- It may represent the removal of suppression of an underlying prothrombotic environment that has remained quiescent during treatment.
- A presumably unstable atherosclerotic plaque may consume tissue factor pathway inhibitor, impairing natural thrombo-resistance.
- Most likely time for reinfarction is 2-4 hours after stopping intravenous heparin.
- Gradual reduction in heparin dose may be preventive.

#### LOW-MOLECULAR-WEIGHT HEPARINS

- Preparations of LMWH contain fewer than 18 saccharides but retain the critical pentasaccharide sequence to form a factor Xa-antithrombin's heparin complex.
- LMWHs have a minimal effect on a PPT.
- LMWHs are derived from unfractionated heparins (UFH) through a chemical and enzymatic depolymerization process resulting in preparations of shorter heparin molecules.
- LMWHs are also indirect thrombin inhibitors that bind AT via the same pentasaccharide sequence found in UFH.
- Anticoagulant effects of LMWHs result from their inhibition of factor Xa and thrombin as well as other factors (XIIa, XIa, and IXa and tissue factor pathway inhibitor).  
They have less inhibitory activity against thrombin than against factor X.
- They are cleared predominantly by renal mechanisms.

Table (17-1): Characteristics of Low-Molecular-Weight Heparins

LMWH	Mean Molecular Weight (Daltons)	Anti-Xa/Anti-IIa Ratio	Half Life (hours)
Enoxaparin (clexane or lovenox)	4200	3.8:1	2.2-5.0
Dalteparin (Fragmin)	6000	2.7:1	2.0-5.0
Nadroparin (fraxiparine)	4500	3.6:1	2.2-3.5

#### Advantages of LMWHs over UFH

- Predictable anticoagulant effect. Their action is not influenced by plasma or tissue proteins.
- Can be administered subcutaneously with high bioavailability.
- Long duration of action. Can be administered once or twice/day.
- Do not require laboratory monitoring for coagulation activity.
- Less likely to induce antibodies and influence platelet function: HIT and HITTS are rare.
- Enhanced anti-Xa activity, relative resistance to the neutralizing effect of platelet factor 4.
- Ability to inhibit factor Xa located on platelet surfaces.
- Inhibition of von Willebrand factor (vWF) resulting in reduction in vWF-platelet adhesion and aggregation.

Table (17-2): Comparison of Unfractionated Heparin and Low-molecular-weight Heparins

UFH	LMWH
- Unpredictable anticoagulant response	- More predictable anticoagulant response
- Requires a PTT monitoring	- No laboratory monitoring required
- Poor bioavailability	- Better bioavailability
- Short half-life	- Longer half-life
- Risk of bleeding complications	- Slightly lower risk of major bleeding
- Risk of thrombocytopenia	- Low risk of thrombocytopenia

#### THERAPEUTIC APPLICATIONS OF HEPARIN

- Acute coronary syndromes.
- Pulmonary embolism.
- Deep venous thrombosis.

- Other indications of heparin:
  1. Hemodialysis.
  2. Cardiac surgery.
  3. Disseminated intravascular coagulation.
  4. Acute arterial embolism.
  5. Prophylaxis against post operative venous thrombosis and pulmonary embolism.
  6. Prosthetic devices e.g. artificial cardiac valves.

#### ACUTE CORONARY SYNDROMES

- Unstable angina and NSTEMI.
- Myocardial infarction (STEMI)..
- Coronary Intervention.

#### Unstable Angina and NSTEMI

##### *Heparin Efficacy*

- Decrease the frequency of angina (by 84-94%).
- Decrease episodes of silent ischemia (by 71-77%).
- Decrease duration of ischemia (by 81-86%).
- Decrease recurrent ischemia with electrocardiographic changes.
- Decrease risk of myocardial infarction.
- Decrease risk of death.

*Current guidelines advocate the combination of aspirin and heparin for initial therapy in unstable angina/NSTEMI.*

- Limitations
  - Increased thrombotic tendency after the cessation of intravenous UFH even in the presence of aspirin (heparin rebound).
  - Other limitations of UFH (protein binding, unpredictable effect, frequent lab monitoring, thrombocytopenia).

##### *Monitoring of UFH*

- Anticoagulant effect of heparin requires monitoring with the activated partial thromboplastin time (aPTT), a test that is sensitive to the inhibitory effects of UFH on thrombin, factors Xa and IXa.

##### *Monitoring of IV Heparin Infusion*

- If the aPTT exceeds twice the patient's control, the rate should be reduced.

- If the aPTT is less than 1.5 times the control, the rate should be increased but should not exceed 44,000 units/24 hours.
- For patients with increased probability of bleeding e.g. recent surgery or trauma, the aPTT should be maintained nearer to 1.5 times the normal value.

### *Monitoring of Heparin Dosage*

- The anticoagulant effect of heparin is titrated by dividing the patient's activated partial thromboplastin time (aPTT) by the mean of the laboratory control aPTT to obtain a ratio of 1.5 to 2.5.
- Measurements should be made 6 hours after any dosage change and used to adjust UFH infusion until the aPPT exhibits a therapeutic level.
- When two consecutive aPPT values are therapeutic, the measurements may be made every 24 hours and if necessary dose adjustment is carried out.
- Any significant change in patient condition (e.g. recurrent ischemia, bleeding, hypotension) required an immediate aPPT determination.
- Serial platelet counts (daily) to monitor for heparin induced thrombocytopenia.  
Mild thrombocytopenia may occur in 10-20% patients.  
Severe thrombocytopenia (platelet count less than 100,000) occurs in 1-2% of patients and appear after 4-14 days of therapy.

### *Dosage Regimens*

- Fixed dose: 5000 unit bolus, 1000 unit/hour initial infusion.
- Weight adjusted: 60 to 70 U/Kg (maximum 5000 U) as initial bolus and 12 to 15 U/Kg/hour (maximum 1000 U/hour) as an initial infusion.
- Weight adjusted regimen provides more predictable anticoagulant than fixed-dose regimen.
- aPPT should be monitored for adjustment of UFH dosage to achieve aPTT in the target range e.g. for a control aPPT of 30 seconds, the target range (1.5 to 2.5 times control) would be 45 to 75 seconds.

### *Other Methods of Heparin Administration*

- Intermittent IV: a dose of 10,000 units initially followed by 5000-10,000 units/4-6 hours.
- Low dose subcutaneous injection: for prophylaxis against thromboembolism 5000 units given 2 hours before surgery and repeated every 8-12 hours until the patient is discharged from hospital.

Table (17- 3): Heparin Adjustment Nomogram for Standard Laboratory Reagents  
(Mean Control aPTT = 26-36 Seconds)

aPTT (sec)	Bolus Dose (U)	Stop Infusion Duration (min)	Rate Change (U/hr)	Repeat aPTT
<49	3000	0	+100	6 hr
40-49	0	0	+50	6 hr
50-70	0	0	No change	Next morning *
71-85	0	0	- 50	Next morning
86-100	0	30	- 100	6 hr
101-150	0	60	-150	6 hr
>150	0	60	-300	6 hr

aPPT= activated partial thromboplastin time. +: increase - : decrease

\* Pending two consecutive therapeutic aPTT 6 hours apart

Note : for aPTTs obtained within 12 hr after initiation of tissue plasminogen activator, do not decrease infusion unless bleeding is significant or aPPT>150 sec. Infusion may be increased if aPPT<50 sec. for aPTTs obtained  $\geq$  12 hr after initiation of thrombolytic therapy, use entire normogram.

Source: Wellis and Hartmann's (2001).

#### *Clinical Factors that Affect the Response to UFH*

- Body weight.
- Age: older patients develop a higher aPTT value, require less UFH.
- Smoking history and diabetes mellitus- a lower aPTT value require more UFH.

#### *LMWH in Unstable Angina and NSTEMI*

- Short-term use of enoxaparin and dalteparin is as effective and safe as unfractionated heparin in reducing the hard endpoints of death and recurrent MI.
- Enoxaparin appears to have a modest superiority over UFH primarily due to reduction in recurrent angina.
- LMWH plus aspirin is the current standard of care in the acute phase of NSTEMI/unstable angina.
- LMWH has a safety profile similar to that of UFH when used in combination with GPIIb/IIIa receptor antagonists.
- Dosage
  - Enoxaparin: 30 mg IV initial bolus immediately followed by subcutaneous injections of 1 mg/kg every 12 hours.
  - Dalteparin: 120 IU/kg bodyweight SC every 12 hours (maximum 10,000 IU bid).

- LMWHs are recommended for the treatment of unstable angina/non-ST- elevation myocardial infarction.
- Clinical trials have demonstrated similar safety with LMWHs compared with unfractionated heparin in the setting of PCI and in conjunction with glycoprotein IIb/IIIa inhibitors.
- LMWHs show promise as antithrombotic agent for the treatment of ST-elevation myocardial infarction.
- LMWHs could potentially replace unfractionated heparin as the antithrombotic agent of choice across the spectrum of ACSs.
- Further study is warranted to define the benefit of LMWHs in certain high-risk subgroups before their use can be universally recommended.

*Wong et al. JAMA, 2003*

#### *Duration of Heparin Therapy*

- 2-8 days or until revascularization.
- LMWH can be given for up to 4 weeks.
- There is only modest non significant reduction in ischemic events with more prolonged LMWH treatment.

#### **Myocardial Infarction (STEMI)**

Heparin reduces reinfarction and mortality in patients with AMI who are treated conservatively, with thrombolytics or with intervention (PCI).

*Conservative treatment in patients* who are not candidates for thrombolytic therapy or intervention (PCI) because of late presentation (more than 12 hours after the onset of chest pain) or because of other contraindications to these approaches.

Heparin mortality reduction is provided by a reduction in reinfarction, stroke and pulmonary embolism.

#### *Heparin Use with Thrombolytics (TPA Type)*

- No benefit when streptokinase is the thrombolytic agent.
- The mechanism appears to be related to a rapid, complete and maintained restoration of coronary blood flow in the infarct-related artery.
- Significant reocclusion rates are a problem with the use of tissue plasminogen activator but not streptokinase.

- Fibrinolytic therapy is accompanied by intensive thrombin generation and activation. The paradoxical coagulant state induced by fibrinolytic therapy is one of the mechanisms responsible for the occurrence of early coronary reocclusion.
- LMWH (enoxaparin) given subcutaneously is superior to UFH as adjunct to the bolus lytic agent tenecteplase (TNK-tPA).  
The early clinical benefit of enoxaparin was lost at one year follow-up and was associated with a 40% increase in severe bleeding (ASSENT-3 trial).  
Longer administration of enoxaparin resulted in lower rates of recurrent ischemic events.
- Current antithrombin therapy following fibrinolytic therapy seems to be optimal with UFH, which is given as a bolus together with the lytic and continued for at least 48 hours (see chapter on thrombolytic agents).
- An alternative therapy following the bolus of UFH, could be subcutaneous administration of enoxaparin until hospital discharge.

Dosage regimen of unfractionated heparin in ST-segment elevation MI in conjunction with tPA-based fibrinolytics

- IV bolus 60 U/kg body weight, maximum 4,000 U followed by
- IV infusion 12 U/kg/h, maximum 1000 U/h, 24-48 hours.  
aPTT at 3,6,12, and 24 hours after treatment onset, aiming at aPTT 50-70 seconds, aPPT 1.5 to 2.5 times control.

This lower dose, weight-based protocol is superior in achieving early therapeutic levels of anticoagulant and reduce the need for dose adjustments.

### Heparin Use in Angioplasty

- Heparin administration is necessary for all forms of angioplasty, however, it does not appear to be advantageous in unstable angina caused by restenosis after coronary angioplasty. This finding underscores the difference in pathophysiology between de novo unstable angina and the cellular proliferation of restenosis.
- UFH is the type used in angioplasty. The benefits and risks of LMWH are not yet established as adjunct to PCI in AMI, but in NSTEMI/unstable angina PCI can be performed effectively and safely with LMWH with or without concomitant GPIIb/IIIa receptor inhibition.
- Enoxaparin is an effective and safe alternative to UFH for the early invasive management of high-risk ACS patients (SYNERGY trial, 2004).
- Dosage regimen of UFH
  1. During direct PCI without GPIIb/IIIa receptor inhibitor.
    - IV bolus 100-175 U/Kg aiming at activated clotting time (ACT) 300-350 seconds.

- IV infusion 10-15 U/kg/hour
- 2. During direct PCI with GPIIb/IIIa receptor inhibitor
  - IV bolus 50-70 U/kg aiming at ACT > 200 seconds.
  - Repeated bolus doses only if complicated, prolonged procedure.
  - Infusion of UFH after the intervention gives no clinical benefit, but increases bleeding risk.

#### Summary of LMWHs

- LMWHs represent a theoretical advance in antithrombotic therapy because of their greater pharmacokinetics predictably and reduced propensity to stimulate platelet aggregation.
- A simplified administration scheme-subcutaneous injections twice daily rather than continuous IV infusion for management of ACS patients.
- There are convincing data that support the use of LMWHs in ACS.
- The safety of enoxaparin plus a GP IIb/IIIa antagonist was comparable to that of UFH plus GP IIb/IIIa antagonist.
- Patients undergoing PCI can be safely managed with enoxaparin and GP IIb/IIIa antagonist, with supplemental use of UFH (NICE-3 study, 2003).
- The use of LMWHs via IV administration allows for the achievement of a rapid and controlled anticoagulation during PCI.
- Level of anticoagulation induced by LMWHs can be measured using the standard ACT test.
- UFH and LMWHs, unlike direct thrombin inhibitors, are at least partially reversible with protamine.
- Unmonitored enoxaparin appears to be better than heparin as an adjunct to coronary thrombolysis with tenecteplase.
- Enoxaparin is superior over UFH in the treatment of ACS patients. Its superiority is sustained over a one-year period.