Learning Objectives

At the conclusion of this activity, participants will be able to:

- Discuss the pharmacology of heparin, low molecular weight heparin, and fondaparinux
- Discuss the indications and contraindications for heparin, low molecular weight heparin, and fondaparinux

Heparin: Mechanism of Action

Most heparin chains can bind both AT and thrombin molecule
Can only form when pentasaccharide chain ≥ 18 saccharides long
Mean molecular weight of UFH = 15,000 daltons (ranges from 6,000-20,000 daltons)
LMWH and fondaparinux exhibit less direct effect on thrombin due to smaller molecular size and weight

Unfractionated Heparin (UFH): Mechanism of Action

Heparin is an electronegative polysaccharide found endogenously in mast cells of the lung, liver, and intestines
Binds directly to Antithrombin (AT), a natural anticoagulant
UFH is an indirect thrombin (Factor IIa) inhibitor
Converts AT to a rapid inactivator of thrombin and Factor Xa
Also inactivates XIIa, XIa, IXa (minor)
Binding mediated by specific pentasaccharide sequence
AT/heparin complex boosts AT function four fold, interrupts intrinsic pathway, specifically conversion of fibrinogen to fibrin

The Coagulation Cascade
Heparin: Pharmacokinetics

Onset of action:
- Subcutaneous: ~30 minutes
- IV: Immediate

Absorption:
- IV: Rapid and complete
- SC: Erratic

Distribution:
- Binds extensively to LDL, globulins (i.e.: AT), and fibrinogen
- Confined to intravascular space
- Does not cross placenta or enter breast milk: considered compatible with pregnancy and lactation

Heparin: Pharmacokinetics

Metabolism
- Primarily hepatic
- Possible reticuloendothelial system involvement
- Preferred vs. LMWH/fondaparinux for use in renal insufficiency as no dosing adjustment needed

Elimination
- t1/2: 3 measures: bioassayed concentration, clotting time, extension of clotting time
- Rule of thumb: 1-2 hours
- Elimination:
  - Unchanged in urine
  - Not dialyzable

Low Molecular Weight Heparin

Similar mechanism of action as heparin, but is a “fractionated” form of UFH
- Primarily binds AT which increases inhibition of Factor Xa
- Mean MW = 4,500 daltons
- Shorter pentasaccharide sequence = less direct anti-thrombin activity

LMWH vs. UFH

“5” denotes native pentasaccharide sequence common to UFH and LMWH
- Both bind AT which potentiates anti-Factor Illa activity
- Must be >6000 daltons (≥18 monosaccharides) to bind both AT and thrombin
- LMWH is too short to concomitantly bind AT and thrombin
LWMH: Pharmacokinetics

Bioavailability: Subcutaneous- 80-95%, but may be affected by high/low body weight
Time to peak: approximately 4 hours
Distribution: Large Vd, average 3-5 liters
Metabolism: Primarily hepatic
Elimination Half life: ranges from 3-7 hours, but may be extended in patients with renal failure

LMWH vs. Heparin

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Take a moment to reflect...

The P&T committee at your institution asks you to compare the advantages and disadvantages of heparin use vs. LMWH. You provide the following information...

Fondaparinux

Synthetic pentasaccharide sequence
Causes AT inhibition of Factor Xa
Similar in size and activity to LMWH

Fondaparinux: Pharmacokinetics

Absorption: Rapid with 100% bioavailability
Time to peak: Subcutaneous
2-3 hours
Distribution: Vd = 7-11 Liters
Elimination half life: 17-21 hours, prolonged in renal dysfunction
Excretion: Unchanged in urine

Fondaparinux vs. LMWH

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Heparin: FDA Approved Indications

Venous Thromboembolism Prophylaxis/Treatment
Acute Coronary Syndromes
Includes: PCI, STEMI, USA/NSTEMI

Heparin: Dosing

Intravenous dosing based on hospital derived nomograms
Weight based initial dosing
Dose adjustments based on aPTT or Anti factor Xa levels
Anti factor Xa most specific for heparin monitoring
Baseline aPTT affected by lupus anticoagulant, factor deficiencies, DIC, liver dysfunction
Smith ML and Wheeler KE study utilizes lower dosing than traditional "80 and 18" dosing and utilizes anti Xa monitoring rather than aPTT
92% of anti Xa results therapeutic within 24 hours on lower dosing vs. 57% in traditional dosing/monitoring study

Heparin Dosing: Special Populations

Heparin Resistance
Patients requiring extremely large doses of heparin to achieve and maintain therapeutic levels
Possible Causes: accelerated heparin clearance, increased heparin binding proteins (e.g.: LDL, fibrinogen), AT deficiency
AT deficiency
Causes of most heparin resistance
Mutation in heparin binding site and/or thrombin binding site
First AT product in US approved Feb 2009
May be beneficial in some high risk patients
**LMWH: FDA Approved Indications**

**Dalteparin**
- Venous thromboembolism prevention (medical illness, hip, abdominal surgery)
- Venous thromboembolism treatment/prevention of recurrence in cancer patients
- Unstable angina (USA) or non Q-wave myocardial infarction

**Tinzaparin**
- Venous thromboembolism treatment
- Preliminary data from IRIS (Innohep® in Renal Insufficiency) study prompted FDA to issue warning advising alternative drugs in elderly patient with renal failure

**Enoxaparin**
- Venous thromboembolism prophylaxis (medical, hip, knee, abdominal surgery)/treatment
- Acute Coronary Syndromes
  - Includes PCI, STEMI, USA/STEMI

**Fondaparinux: FDA Approved Indications**

- Venous thromboembolism prophylaxis/treatment

**LWMH: Dosing**

**Dalteparin**
- DVT prophylaxis
  - 5000 units SC daily

**Tinzaparin**
- DVT +/- PE treatment: 175 Anti Xa international units/kg SC daily

**Enoxaparin**
- DVT/PE treatment: 1 mg/kg SC BID or 1.5mg/kg SC daily, 1 mg/kg SC daily for CrCl <30ml/min
- DVT/PE medical prophylaxis: 40 mg SC daily, 30 mg SC daily for CrCl <30ml/min

**Fondaparinux: Dosing**

- DVT/PE prophylaxis (adults at least 50 kg): 2.5mg SC daily
- DVT/PE treatment
  - <50 kg = 5 mg SC daily
  - 50-100 kg = 7.5mg SC daily
  - >100 kg = 10 mg SC daily

**Heparin: Contraindications**

- Hypersensitivity to heparin or any component of the formulation (including pork products)
- Severe thrombocytopenia, HIT
- Uncontrolled active bleeding (except when due to disseminated intravascular coagulation - DIC)
- Suspected intracranial hemorrhage (ICH)
- Inadequate laboratory monitoring available
LMWH: Contraindications

- Hypersensitivity to heparin or LMWH products and components (includes pork allergies)
- Active HIT or history of HIT
- Active bleeding

*Boxed Warning: Patients undergoing epidural or spinal anesthesia are at increased risk of spinal hematoma and paralysis*

Fondaparinux: Contraindications

- Hypersensitivity to fondaparinux
- CrCl < 30ml/min
- Prophylaxis doses in patients weighing < 50 kg
- Active bleeding
- Bacterial endocarditis

*Thrombocytopenia in vitro positive for antiplatelet antibodies in the presence of fondaparinux*

*Boxed Warning: Patients undergoing epidural or spinal anesthesia are at increased risk of spinal hematoma and paralysis*

CHEST Guidelines: Thromboprophylaxis

In patients admitted to hospital with **acute medical illness**, thromboprophylaxis with LMWH, low dose UFH (LDUH), or fondaparinux is recommended (Grade 1A)

*On admission to ICU, it is recommended all patients be assessed for VTE risk and that most receive thromboprophylaxis (Grade 1A)*

CHEST guidelines: Treatment of DVT/PE

**Objectively confirmed DVT** = LMWH, IV UFH, monitored SC UFH, fixed-dose SC UFH, or SC fondaparinux (all Grade 1A)

**High clinical suspicion of DVT** = treat with anticoagulants while awaiting test outcomes (Grade 1C)

**Acute DVT** = LWMH as an outpatient if possible, rather than treatment with IV UFH (Grade 1C)

**Patients with acute DVT and renal failure** = UFH suggested over LMWH (Grade 2C)

CHEST Guidelines: Treatment of DVT/PE

**Objectively confirmed PE** = LMWH, IV UFH, monitored SC UFH, fixed-dose SC UFH, or SC fondaparinux (all Grade 1A)

**High clinical suspicion of PE** = treat with anticoagulants while awaiting test outcomes (Grade 1C)

**Acute non-massive PE** = initial treatment with LMWH over IV UFH (Grade 1A)

**Massive PE, concerns about SC absorption, thrombolysis planned, severe renal failure** = IV UFH preferred (Grade 2C)

CHEST Guidelines: ACS/NSTEMI

In addition to other recommended anticoagulant measures (i.e.: aspirin, clopidogrel, GPIIb/IIIa inhibitors):

**All patients**: recommend starting UFH, LMWH, bivalirudin, or fondaparinux (Grade 1A)

For patients undergoing an **early invasive strategy**: recommend UFH (and GPIIb/IIIa inhibitor) over LMWH or fondaparinux (Grade 1B)

For patients undergoing **conservative or delayed invasive strategy**: recommend fondaparinux over enoxaparin (Grade 1A) and LMWH over UFH (Grade 1B)
CHEST guidelines: Acute STEMI

In addition to aspirin and antiplatelet therapies, recommend UFH, enoxaparin, or fondaparinux (including patients receiving fibrinolysis, primary PCI, or patients not receiving reperfusion therapy) (Grade 1A)

References

- "Dalteparin." In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2010.
- "Enoxaparin." In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2010.
- "Heparin." In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2010.
- "Tinzaparin." In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2010.