Parenteral Antithrombotics and Thrombolytic Therapy

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DISCLOSURES

Off-Label Usage
  • Apizaban

Interests
  • None
Mechanism of Action for Heparin Family
Indirect Inhibition - Requires ATIII

Anti-Thrombin Activity
Heparin > LMWH
Mechanism of Action for Heparin Family
Indirect Inhibition - Requires ATIII

Anti-Xa Activity
Fondaparinux > LMWH > Heparin

ATIII BINDING
Mechanism of Action for Heparin Family
Indirect Inhibition - Requires ATIII

CHAIN LENGTH DETERMINES PROFILE

- Less than 18-saccharides = anti-FXa only
- 18 or more saccharides = anti-IIa + anti-Fxa
Source Of Heparin

- Biologic Product - “infectious??”
- Variability Lot to Lot - only 1/3 of heparin in a vial is active
- “Refined” to LMWH - all brands differ in characteristics/profile
Saturable Heparin Clearance

1. Binding to endothelium, macrophages, plasma proteins

2. Patient size correlates with endothelial binding

3. Physiologic conditions effect macrophages -- acute phase reactants

Sub-saturating dose rapidly cleared
So, how do use dose heparin in a 150kg patient. Should bolus be “capped” at 5,000 units?
Tidbits Regarding Heparin Therapy

- Bolus/infuse by nomogram
  - Use best dry weight
  - Endothelium in adipose, not in water
  - 150kg = bolus (80/kg) 12,000 units & drip (18/kg) 2700 units (dry weight)

- Patient may be sensitive or resistant to heparin, monitor PTT at least every 6-8 hours until therapeutic then once a day

- Dose may decrease as “acute phase reaction” of patient clears
LMW Heparin Clearance

- Weak Binding to endothelial cells, macrophages, and other plasma proteins
- Kidney major site of clearance - slower
Favorable LMWH Characteristics

- Better bioavailability allowing for predictable anticoagulant effect at a given dose and less need for laboratory monitoring.
- Longer plasma half-life therefore longer dosing interval.
- Less effect on the hemostatic properties of the endothelium and platelets perhaps accounting for decreased hemorrhagic potential.
Myths Regarding LMWH

1. Never need monitoring – **WRONG!**
   - Patients with changing kidney function
   - Very large, very small, and pregnant patients

2. Bleeding is not a problem with LMWH - **WRONG!**
   - Treatment dose - bleeding equivalent to heparin
   - LMWH only partially reversible with protamine
   - LMWH have longer t1/2 – longer bleeding risk
Fondaparinux (ARIXTRA) Indirect Inhibition Factor Xa - Requires ATIII

Synthetic Pentasaccharide Antithrombin Binding Site Only

ATIII

Factor X

Pure Anti-Xa Activity
Kidney clearance almost exclusively
The longer the chain
- Greater antithrombin activity
- More charge = better target for protamine
- Greater binding to endothelium/macrophages with rapid clearance
- More effect on PTT

The shorter the chain
- OPPOSITE E OF ALL POINTS ABOVE
How Does Protamine Work

Charge interaction creates complex and heparin no longer free to bind other proteins.
<table>
<thead>
<tr>
<th>PROTAMINE REVERSAL</th>
<th>ANTI IIa:ANTIXa</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNFRACTIONATED HEPARIN</td>
<td>(-) (-) (-) (-) (-) (-) (-) (-) (-) (-) (-) (-) (-) (-) (-) (-) (-) (-) (-) (-) (-) 1:1</td>
</tr>
<tr>
<td>Excellent</td>
<td>DALTEPARIN</td>
</tr>
<tr>
<td>Some</td>
<td>ENOXAPARIN</td>
</tr>
<tr>
<td>Minimal</td>
<td>FONDAPARINUX</td>
</tr>
<tr>
<td>Forget it</td>
<td></td>
</tr>
</tbody>
</table>
What Can We Do To Reverse Anticoagulation

- The Heparin/pentasaccharide family - PROTAMINE
  - Heparin is the only rapidly reversible drug
  - LMWH may be 20-30%, Fragmin>Lovenox>Arixtra
  - CAUTION – Do you know your protamine?
    - Has weak anticoagulant effect AND prolongs PT/PTT at high dose
    - Giving high dose protamine to “MAYBE” reverse Lovenox / Arixtra may worsen coagulopathy
    - Protamine has a shorter half-life and interaction with Heparin/LMWH is reversible; therefore get rebound anticoagulant effect as protamine cleared faster than high dose heparin or LMWH
### Indirect Thrombin and/or FXa Inhibitors

<table>
<thead>
<tr>
<th>Heparin (Fondaparinux)</th>
<th>LMWH* (Arixtra)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical hours</strong></td>
<td>1-6 hours</td>
</tr>
<tr>
<td><strong>Effect</strong></td>
<td>12-24*</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Endothelium</td>
</tr>
<tr>
<td><strong>Δ T ½ disease</strong></td>
<td>Higher dose</td>
</tr>
<tr>
<td><strong>longer t ½</strong></td>
<td>Kidney disease</td>
</tr>
<tr>
<td><strong>Reversible</strong></td>
<td>Protamine</td>
</tr>
<tr>
<td></td>
<td>Protamine*</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>MINIMAL</td>
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*Indications and characteristics vary for three available products
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<tr>
<td><strong>Fondaparinux</strong> <em>(Arixtra)</em></td>
<td></td>
</tr>
<tr>
<td>Monitor</td>
<td>aPTT</td>
</tr>
<tr>
<td>Xa assay</td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>+++</td>
</tr>
<tr>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>HITT</strong></td>
<td><strong>YES</strong></td>
</tr>
<tr>
<td><strong>NO??</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Binds PF4</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Indications and characteristics vary for three available products
WHAT OTHER DRUGS ARE APPROVED FOR ANTICOAGULATION
Direct Thrombin Inhibitors

ARGATROBAN
Reversible binding to active site

BIVALIRUDIN
Binding activates enzyme engineered into drug that breaks down drug
Direct Thrombin Inhibitors

- Do **NOT** need cofactor for activity-direct inhibitor
- Do **NOT** bind to endothelium or other proteins
- Do **NOT** have known drug interactions
- Do **NOT** cause thrombocytopenia
- ARE **NOT** REVERSIBLE
- **DO** inhibit clot bound thrombin
- **DO** effect platelet function
## Direct Thrombin Inhibitors (DTI)

<table>
<thead>
<tr>
<th></th>
<th>Argatroban</th>
<th>Bivalirudin</th>
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</thead>
<tbody>
<tr>
<td><strong>Product peptide</strong></td>
<td>Synthetic arginine peptide</td>
<td>Synthetic analogue</td>
</tr>
<tr>
<td><strong>FDA PTCA</strong></td>
<td>Approved HITT</td>
<td>Approved</td>
</tr>
<tr>
<td><strong>MW</strong></td>
<td>506</td>
<td>2180</td>
</tr>
<tr>
<td><strong>Clinical Effect</strong></td>
<td>Direct anti-IIa reversible</td>
<td>Direct anti-IIa self-destructs</td>
</tr>
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## Direct Thrombin Inhibitors (DTI)

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<tr>
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<th>Argatroban</th>
<th>Bivalirudin</th>
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<tbody>
<tr>
<td>Monitor</td>
<td>aPTT 1.5-3.0</td>
<td>ACT 250-350</td>
</tr>
<tr>
<td>Effects PT</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Bleeding</td>
<td>++</td>
<td>++</td>
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# Direct Thrombin Inhibitors

<table>
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<th>Bivalirudin</th>
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<tr>
<td><strong>T 1/2</strong></td>
<td>39-51 min</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Liver disease</td>
</tr>
<tr>
<td><strong>D T 1/2</strong></td>
<td>Hours</td>
</tr>
<tr>
<td><strong>Reversible</strong></td>
<td>NO</td>
</tr>
</tbody>
</table>

- **Argatroban**
  - Half-life: 39-51 minutes
  - Excretion: Liver disease
  - Duration: Hours
  - Reversible: No

- **Bivalirudin**
  - Half-life: 25 minutes
  - Excretion: Kidney disease
  - Duration: 3.5 hours
  - Reversible: No – self destructs
Treatment Pitfalls - Famous Last Words!

I’ll just reverse the drug if he bleeds...
Plasma

Are Direct Thrombin Inhibitors Reversible?
Are Direct Thrombin Inhibitors Reversible?

Plasma

PCC or rFVIIa
Are Direct Thrombin Inhibitors Reversible?

- Dialysis
- Protamine
- Plasma
- rFVIIa
- PCC
Are Direct Thrombin Inhibitors Reversible?

- Plasma
- Dialysis
- Protamine
- rFVIIa
- PCC
Are Direct Thrombin Inhibitors Reversible?

- Plasma
- Protamine
- Dialysis
- Vitamin K
- PCC
- rFVIIa
Are Direct Thrombin Inhibitors Reversible?

- Plasma
- Protamine
- Dialysis
- Vitamin K
- Cryoprecipitate
Are Direct Thrombin Inhibitors Reversible?
Patient is on DTI not heparin I’ll do hypercoaguuable w/u before Warfarin is started
Patient is on DTI not heparin I’ll do hypercoag w/u before Warfarin is started

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**Treatment Pitfalls - Famous Last Words!**

DTIs EFFECT ALL CLOT BASED ASSAYS – Beware False Results

- FIBRINOGEN!
- PT/PTT
- RVVT
- Silica Clot time
- StaClot
- Protein C activity
- Protein S activity
- Reptilase
- Thrombin clot time

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INTERN

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Guidelines for Conversion To Warfarin From Argatroban

- If INR is not in therapeutic range on warfarin, resume DTI.
- If INR is >4.0, stop Argatroban.
- Initiate warfarin using expected daily dose and continue Argatroban. NO WARFARIN LOADING DOSE.
- Measure INR daily.
- If INR is ≤4.0, continue both drugs.
- If INR is >4.0, stop Argatroban.
- Repeat INR 4-6 hours later.
- If INR is in therapeutic range on warfarin, continue warfarin monotherapy.
- If INR is not in therapeutic range on warfarin, resume DTI.
Plasminogen binds to fibrin in blood as fibrin polymerizes. Number of plasminogen binding sites controlled by Thrombin Activator Fibrinolysis Inhibitor (TAFI). The more binding sites, the more plasminogen, the faster clot lysis.

TAFI decreases # of binding sites
Fibrin settling on intact endothelium starts fibrinolytic process.
When Fibrin settles on Endothelium, it provokes Endothelium to release of tPA and Single Chain Urokinase. Fibrin catalysis its own destruction.
tPA and/or Scu-PA “clips” plasminogen and creates the active enzyme Plasmin.
Plasmin clips off pieces of fibrin releasing the smallest subunit that cannot be broken, the d-dimer.
As tPA released from Fibrin it is bound and neutralized by Plasminogen Activator Inhibitor (PAI) and as Plasmin released it is bound and neutralized by alpha 2 plasmin inhibitor (aka alpha 2-antiplasmin)
Alteplase (Activase®; rtPA)
- recombinant form of human tPA – rare immune response
- short half-life (~5 min)
- administered as an intravenous bolus followed by an infusion.

Retaplace (Retavase®)
- genetically engineered - contains fibrin binding sites and active site
- smaller derivative of recombinant tPA
- increased potency and is faster acting than rtPA
- administered as IV bolus injections
Tenecteplase (TNK-tPA)
  - longer half-life
  - greater binding affinity for fibrin than rtPA
  - administered by IV bolus
  - greater resistance to PAI-1
INDICATIONS FOR THROMBOLYTIC THERAPY

- Accepted Indications
  - Acute myocardial infarctions
  - Thrombotic stroke within 3 hours
  - Acute peripheral arterial occlusive disease
  - Massive pulmonary embolism with hemodynamic instability
INDICATIONS FOR THROMBOLYTIC THERAPY

QUESTION

Does therapy do more than provide accelerated clot lysis and short-term physiologic improvement?
THROMBOLYTIC THERAPY
CONTRAINDICATIONS

ABSOLUTE

- History of hemorrhagic stroke
- Major internal bleeding in previous 6 months
- Intracranial or intraspinal neoplasm
- Recent (<2mon) intracranial surgery
THROMBOLYTIC THERAPY CONTRAINDICATIONS

RELATIVE

- Surgery or biopsy in the preceding 10 days
- Hypertension (>200 systolic, >110 diastolic)
- Thrombocytopenia (< 100,000)
- Nonhemorrhagic stroke within 2 months
- Presence of a bleeding disorder
Patient selection

- Catheter directed vs systemic, mostly catheter-directed
- Patients with massive iliofemoral or proximal femoral DVT with risk of limb compromise best candidate
- Ongoing studies “ATTRACT TRIAL” to determine benefit
Inadequate fibrinolytic response

- May occur in patients with baseline or acquired low plasminogen levels (i.e., consumed by therapy)
- Patients with old clot (> 14-21 days) less responsive
- Premature termination of therapy - monitor progress
  - Stop therapy at 24 hrs if no lysis has occurred
  - Continue therapy after 24 hours if partial lysis
PE - Indications For Thrombolytic Therapy

- Massive acute pulmonary emboli
- Patient hypotensive
- Patient hypoxic despite high levels of oxygen
- Echocardiographic evidence of right ventricular failure?
- Non-invasive treatment results in less bleeding
  - ie avoid angio/catheter directed therapy
Laboratory Evaluation In Thrombolysis

- **Common laboratory findings**
  - low plasma fibrinogen
  - elevated fibrinogen degradation products inclusive of d-dimer
  - reduction in platelet count
  - Prolongation of PT and PTT

- No laboratory finding predicts bleeding risk
Risk Factors For Bleeding

- CNS bleeding more common in elderly (>70 years)
- Trend towards HTN as a risk factor for CNS bleed
- Dose effect - CNS bleed lower with 100mg vs 150mg
- CVA/TIA patients have greater risk of CNS bleed
- Co-morbidity especially liver or kidney disease
- ASA, NSAID, B-blockers, nitrates may increase risk
- Heparin increases bleeding but improves mortality
Treatment Of Bleeding After Thrombolytic Therapy

- Apply local control measures, i.e., pressure to site
- Reverse heparin with protamine if applicable
- Obtain coag tests to guide replacement therapy
  - PT / aPTT to determine if plasma needed to replace clotting factors destroyed by plasmin (FV, FVIII)
  - Fibrinogen level to determine if cryoprecipitate needed to replace fibrinogen destroyed by plasmin
  - Platelet count - if count < 100,000 then transfuse. Platelets are activated by plasmin
- Avoid additional invasive procedures
Tune in again for more
- Cascade of Caveats -
during the next COAG HOUR