IIb/IIIa, Vitamin K, and Direct Thrombin Inhibition in Cardiology

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Objectives

- Review the pharmacology, kinetics, indications, and monitoring parameters of IIb/IIIa inhibitors and warfarin
- Discuss strategies of reversing over anticoagulation with warfarin
- Discuss the potential advantages of direct thrombin inhibition and the investigational agent, ximelagatran

What is a IIb/IIIa inhibitor?

- Abciximab (monoclonal antibody)
- Eptifibatide
- Tirofiban
  - direct occupancy of the GP IIb/IIIa receptor by a monoclonal antibody or by synthetic compounds mimicking the KGD or RGD sequence for fibrinogen binding prevents platelet aggregation

The 3 Steps of Platelet Aggregation

1. Adhesion
2. Activation
3. Aggregation

Platelet-fibrin clot

Video of a IIb/IIIa inhibitor “in action”

So when and how do we use IIb/IIIa inhibitors???

Unstable Angina and non-ST-segment elevation MI

- All agents are indicated with aspirin, a heparin, and clopidogrel to patients in whom catheterization and PCI are planned. The IIb/IIIa antagonist may be administered just prior to PCI.¹
  - Tirofiban has fallen out of favor based on TARGET trial²
- Eptifibatide or tirofiban are used with aspirin and a heparin product in patients with continuing ischemia, an elevated troponin or with other high-risk features in whom an invasive strategy is not planned.¹
  - Cost effectiveness of use in non-high risk patients is questionable¹
  - Abciximab should only be used when an early invasive strategy is planned (within 24 hours)¹

²NEJM 2001; 344: 1888-1894.

Acute MI

- Primary PCI
  - Abciximab is the preferred IIb/IIIa inhibitor in this setting³
- With fibrinolytics
  - Controversial, may help, but also more bleeding²³
- After fibrinolytics in conjunction with PCI
  - Controversial, no good data yet

Tirofiban (Aggrastat®) and Eptifibatide (Integrilin®)

- Small molecules
- High specificity for GP IIb/IIIa receptor
- Blocks fibrinogen binding and inhibits platelet aggregation
- Short acting and REVERSIBLE

¹JACC 2003;42: 1879-85.
Tirofiban and Eptifibatide Absorption and Metabolism

- Tirofiban produces 90% platelet inhibition within 30 minutes of loading dose
- Eptifibatide produces significant platelet inhibition in 1 hr
- Half-life 2 hours for both
- Platelet function returns to near-baseline 4 to 8 hours after discontinuation for both
- Dose reductions for renal dysfunction necessary for both

Tirofiban and Eptifibatide Lab Monitoring

- Pre treatment
  - SCr, Hct, Hgb, and platelets
- 6 hours after bolus and then daily
  - Hgb, Hct and platelets

Abciximab (Reopro®)

- Monoclonal antibody
- High specificity for GP IIb, IIIa receptor
- Blocks platelet cross-linking by fibrinogen
- Longest-acting and NOT reversible

Reopro Absorption and Metabolism

- Produces 80% platelet inhibition in 2 hours
- Half-life 8-12 hrs
- Irreversibly bound
- Remains in circulation for up to 10-15 days
- Platelet recovery 48 hrs after discontinuation
- Platelet transfusion to reverse effects

Reopro Lab Monitoring

- Pre treatment and next AM
  - Hct, Hgb, and platelets
- 2 hours after bolus
  - Platelets

Reopro Adverse Effects

- Thrombocytopenia
  - Higher frequency compared to other GP IIb/IIIa inhibitors
  - Resolves spontaneously or platelet transfusion
  - Considered severe when platelets < 50,000
    - 4% incidence with readministration
- Acute profound thrombocytopenia
  - Platelets < 20,000 within 24 hours after initiation
  - 0.7% incidence
  - Discontinue infusion immediately
  - Resolve with platelet transfusion
IIb/IIIa Contraindications

- Active internal bleeding
- Known hypersensitivity
- Intracranial hemorrhage/neoplasm
- CVA (varies by drug)
- Arteriovenous malformation or aneurysm
- Recent major surgery / trauma
- Severe uncontrolled HTN
- Thrombocytopenia < 100,000
- Dialysis (eptifibatide)
- History of vasculitis (abciximab)
- Acute pericarditis (tirofiban)

Summary Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Abciximab</th>
<th>Eptifibatide</th>
<th>Tirofiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half Life</td>
<td>8-12 hr</td>
<td>2 hr</td>
<td>2 hr</td>
</tr>
<tr>
<td>Specificity</td>
<td>High/Irreversible</td>
<td>High/Reversible</td>
<td>High/Reversible</td>
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<tr>
<td>Dose</td>
<td>0.25 mg/kg bolus, 0.125 mcg/kg/min for 12-24 hours (PCI)</td>
<td>180 mcg/kg bolus X 2 (max 22.6 mg), 2 mcg/kg/min (max 15 mg/hr) for 18-24 hours (PCI)</td>
<td>0.4 mcg/kg/min bolus; 0.1 mcg/kg/min for 48-96 hours (ACS medical therapy)</td>
</tr>
<tr>
<td>Indication</td>
<td>PCI</td>
<td>PCI/ACS Med Mgt</td>
<td>PCI/ACS Med Mgt</td>
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<tr>
<td>Dose Adjustment</td>
<td>None</td>
<td>CrCl &lt; 50 mL/min Inf ; 1 mcg/kg/min (7.5 mg/hr max)</td>
<td>CrCl &lt; 30 mL/min % dose for both load and infusion</td>
</tr>
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Warfarin

- Synthesized at University of Wisconsin
- Derived from Wisconsin Alumni Research Foundation and ARIN from “heparin”
- Reversibly binds and inhibits enzymes which convert inactive vitamin K to active vitamin K
- Decreases production of vitamin K-dependent clotting factors II, VII, IX, and X
- Decreases production of natural anticoagulants protein C and S

Rat poison!

Clotting Cascade

Vitamin K-Dependent Clotting Factors

- Synthesis of Functional Coagulation Factors
**Vitamin K Mechanism of Action**

![Diagram of Vitamin K Mechanism of Action]

**Clotting Cascade**

![Diagram of Clotting Cascade]

**Warfarin Pharmacokinetics**

- Racemic mixture of R- and S-warfarin
  - S-warfarin 5x more potent, but eliminated more rapidly
- Well absorbed (100% bioavailability)
- Highly protein bound to albumin
- Metabolized by:
  - S-warfarin-2C9
  - R-warfarin-1A2, 2C19, 3A4
  - You must know and understand this for drug interactions!!!!
- Average half-life 36-42 hours

**Prothrombin Time (PT)**

- Responsive to depression of factors II, VII and X
- Initial prolongation of PT due to factor VII depression
- Antithrombotic effect requires 5-7 days of treatment; LOADING DOSES SHOULD NOT BE USED!

<table>
<thead>
<tr>
<th>Component</th>
<th>Time</th>
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<tbody>
<tr>
<td>II</td>
<td>60 hrs</td>
</tr>
<tr>
<td>VII</td>
<td>6 hrs</td>
</tr>
<tr>
<td>IX</td>
<td>24 hrs</td>
</tr>
<tr>
<td>X</td>
<td>40 hrs</td>
</tr>
<tr>
<td>Protein C</td>
<td>6 hrs</td>
</tr>
<tr>
<td>Protein S</td>
<td>72-96 hrs</td>
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</tbody>
</table>

**How do we monitor warfarin therapy?**

- Thromboplastin and the PT time
  - Sensitive to depletion of II, VII, and X
- Prepared from various tissues and recombinant technology
- Affects sensitivity
- Results in variability of PT results
- WHO thromboplastin
- $\text{INR} = \left(\frac{\text{PT Patient}}{\text{PT Control}}\right)^{\text{ISI}}$
  - ISI = international sensitivity index

![Diagram of Warfarin Mechanism of Action]
Dosing: Initiation and Maintenance

• When a rapid effect is required, heparin should be given concurrently with warfarin for at least 4 days. Heparin treatment is usually discontinued when the INR has been in the therapeutic range on two measurements taken 24 hours apart.

• Commence therapy with an average maintenance dose of 5 mg
  Starting doses < 5 mg might be appropriate in elderly, in patients with impaired nutrition or liver disease, and in patients at high risk of bleeding.

What is the therapeutic range for warfarin?

• 2-3 (target 2.5) for the vast majority of indications
• 2.5-3.5 for some mechanical heart valves
  – Mitral valves
  – Aortic valves with atrial fibrillation

Warfarin Indications

• Atrial fibrillation
• DVT/PE treatment/prevention
• Heart Valves
• Severe cardiomyopathy
• Acute myocardial infarction
• Stroke
• Peripheral vascular disease
• Maybe a few others…..

Warfarin

Management of Nontherapeutic INRs

• Fluctuations may be due to a number of variables:
  ✓ Changes in vitamin K₁ intake
  ✓ Changes in vitamin K₁ or warfarin absorption
  ✓ Changes in vitamin K₁-dependent coagulation factor synthesis or metabolism
  ✓ Patient compliance issues
  ✓ Other effects of undisclosed concomitant drug use

High INR concepts

• FFP or prothrombin complex concentrate must be used whenever immediate reversal is needed
  – Bleeding, emergent high bleeding risk surgery
• Vitamin K can be used to reverse warfarin, but takes 24 hours to have good effect
  – Oral is the preferred route of administration
  – Do not overreact to high INR's, high doses lead to resistance!
High INR concepts

• INR < 5 without significant bleeding, lower the dose or omit the dose and resume at a lower dose when INR is at therapeutic level
• INR 5-9 without significant bleeding, omit next 1-2 doses of warfarin and lower dose, or omit and give 1-2.5 mg of po vit K if patient is at higher risk of bleeding or give 2-4 mg po vit K if more urgent reversal is needed to facilitate surgery
  – May repeat 2 mg po if needed for urgent situations

High INR concepts

• INR > 9 without bleeding, omit warfarin and give 3-5 mg of oral vit K
• For INR > 20 and serious bleeding, give 10 mg of vitamin K by slow IV infusion and give FFP or prothrombin complex concentrate
• For life-threatening bleeding, give 10 mg of vitamin K by slow IV infusion and give prothrombin complex concentrate

Final Warfarin Issues

• Education, education, education!!!
  – Why they are on it
  – Monitoring/Travel
  – Booze
  – Compliance, missed doses, not doubling up
  – Drug interactions
  – Signs of bleeding and thrombosis
  – Contact sports
  – Diet/consistency
• Generic warfarin is okay
• And so much more…see www.coumadin.com

Why not directly inhibit thrombin?

Direct Thrombin Inhibitors

• IV agents
  – Bivalirudin mainly used in limited fashion for PCI
  – Argatroban mainly used by IV infusion for HIT
• Oral agent
  – Ximelagatran
  – Not yet approved, applications pending at FDA for prevention of stroke with a. fib., secondary prevention of DVT/PE, and total knee replacement surgery DVT prophylaxis

Potential advantages of ximelagatran over warfarin

• Fixed dosing
• Rapid onset/offset of effect
• Predictability
• Wide therapeutic window
• Could be used to treat HIT
• May not need to overlap a heparin
• No INR’s needed
A 56 year-old man is admitted to the hospital with unstable angina. The MD has ruled out acute MI, but the patient does demonstrate ST segment depression, ongoing pain, and has positive cardiac markers. The cardiologist controls his pain with morphine and decides the patient is stable enough to pursue PCI in the morning. (He has already started all other appropriate medications.) He calls to ask which of the IIb/IIIa agents can be used in this situation based on the literature. He has normal renal function.

– What is your response?
– What if eptifibatide was chosen and the patient had a CrCl < 50?
– What if the patient was more stable and would not be undergoing a PCI in < 24 hours? What agent would you choose?
– What practitioner aside from the cardiologist do you think is integral to designing clinical pathways to standardize how the above situation is handled and helps decide which IIb/IIIa inhibitors are on formulary?

A 70 yo female is 20 days s/p coronary bypass grafting. She has had numerous setbacks in her recovery and her latest problem is the development of a deep vein thrombosis. After two days of 5 mg of warfarin, her INR jumps to 11. She is not bleeding. The surgeon orders 2 units of FFP.

– Is this appropriate?
– What would you advise as the patient’s pharmacist?

A 28 yo college student presents to your warfarin clinic for her routine INR. She has a history of mechanical mitral and aortic valve replacements. She take 4 mg of warfarin daily and her INR’s are consistently in range. Her INR result is 4.2. She just returned from spring break in Mexico.

– What might be the reason for her high INR?
– Should she get vitamin K?
– Should we lower her chronic warfarin dose?