Hemostasis/Thrombosis IV

Antithrombotic Therapy

Mainstay of battle against thromboembolic disease

Hot area of new drug research

Cannot inhibit clot formation without increased risk of hemorrhage

2nd highest cause of iatrogenic complications

2nd most common cause of increased hospital stays
Antithrombotic Therapy

- Hemorrhage is consequence of overaggressive therapy
- Thrombosis is consequence of underaggressive therapy
- Always a balance between risk of thrombosis (for which you are giving the drug) vs. risk of hemorrhage

Antithrombotic Therapy

- Antiplatelet agents
  - Principally used for preventing/treating arterial thromboembolic disease
- Anticoagulants
  - Principally used for preventing/treating venous thromboembolic disease
- Thrombolytic agents
  - Used for dissolution of thrombi
Antiplatelet Therapy

- Paralyze platelet function
- Cyclooxygenase inhibitors
  - Irreversible – Aspirin
  - Competitive inhibitors – Non-steroidal antiinflammatory drugs
- Dipyridamole
- GP IIb/IIIa inhibitors
- ADP receptor inhibitors
  - Ticlopidine
  - Clopidogrel

Aspirin

- Covalently modifies cyclooxygenase; irreversibly inhibits the enzyme
- Since platelets have no protein synthetic mechanism, cannot correct defect caused by modification of cyclooxygenase
- Blocks primary wave of platelet aggregation; NOT secondary wave
- If enough normal platelets to initiate primary aggregation, ASA poisoned platelets can be recruited into platelet plug formation
Non-steroidal Antiinflammatory Drugs

- Competitive inhibitors of cyclooxygenase (drug must be in system to be effective)
- Many block both primary & secondary waves of platelet aggregation
- As such, inhibit clot formation to a greater extent than does ASA
- Blocks ASA effects on platelets; ASA should be taken first

Dipyridamole

- ? Mechanism of action
  - Probably increases cAMP production
- Decreases platelet aggregation
- Enhances aspirin’s effect on platelet aggregation
Glycoprotein IIb/IIIa Inhibitors

- All interfere with fibrinogen-induced platelet aggregation
- 2 classes – Fab fragments (abciximab) & Small molecule inhibitors (tirofiban & eptifibatide)
- Extremely potent – Essentially render platelet count functionally zero
- Used to block immediate restenosis following cardiac intervention
- Major cause of thrombocytopenia
- Current drugs too potent for long-term use

ADP Receptor Inhibitors

- Block ADP’s stimulation of platelet aggregation; competitive inhibitors
- 2 drugs currently approved:
  - Ticlopidine – Rarely used
  - Clopidogrel
- Both long-acting; both inhibit transfused platelets as well as patient’s platelets
- No reversing agent
- Used chronically to prevent restenosis post-vascular interventions
Anticoagulant Therapy

- Inhibitors of coagulation cascade
- Useful both for prophylaxis against TE disease & treatment of TE disease
- Lower doses required for prophylaxis
- All agents prevent propagation of clot; none dissolve clot already formed

Available Anticoagulants

- Older agents
  - Heparin (Parenteral)
  - Warfarin (Oral)
- Now, FDA approved (in addition to the above):
  - 4 low molecular weight heparins (3 available in US)
  - 1 heparinoid (not available in US)
  - 1 Factor Xa inhibitor
  - 3 direct thrombin inhibitors
- More to come
Heparin/Heparin Derivatives

- All act to potentiate antithrombin III’s inactivation of the active enzymes of the clotting cascade
- Chemical catalysts – Not consumed in reactions themselves
- All are useful in both preventing thrombosis & treating thromboembolic disease

ANTITHROMBIN III – Mechanism of Action
Unfractionated Heparin

Advantages

- Long track record
- Dirt cheap
- Clearly effective for treatment & in some prophylaxis settings
- Fully reversible with protamine
- Short half-life

Disadvantages

- Short half life – Requires continuous infusion
- Variable bioavailability
- Monitoring required for treatment of thromboembolic disease
  - To ensure attainment of therapeutic anticoagulation, rather than to prevent bleeding
- Higher risk of complications
  - Especially thrombocytopenia with paradoxical thromboembolic disease
Low Molecular Weight Heparins

**Advantages**

- Higher bioavailability; makes dosing without monitoring a reality (except in renal disease, morbid obesity, cachexia)
- Longer half-life; therefore can be given subcutaneously 1-2x/day
- Much lower (but not 0) risk of *de novo* thrombocytopenia
- At least as effective for treatment; more effective for high risk prophylaxis than heparin

**Disadvantages**

- More expensive than heparin
- Longer acting, and only partially reversible with protamine
- Renally excreted, making dosing problematic in renal disease
- Cross-reactive with HIT causing antibodies
- Much more effective for prophylaxis if given pre-op
- All carry black box warning vs. use with regional anesthesia
Low Molecular Weight Heparins (US)

- Enoxaparin (Lovenox®) – Approved for VTE prophylaxis, VTE treatment, acute coronary syndrome
- Dalteparin (Fragmin®) – Same as enoxaparin RE: approvals, except for VTE treatment
- Tinzaparin (Innohep®) – Approved for treatment of VTE
- Ardeparin (Normiflo®) – Not being marketed in US
- All behave similarly, but dosing of each is different

FACTOR Xa INHIBITOR

- Fondaparinux (Arixtra®) – Semisynthetic sulfated pentasaccharide; active moiety of heparin
- Only inhibits factor Xa
- Bioavailability virtually 100%; can be given QD
- No thrombocytopenia seen in trials (does not bind to platelet factor IV)
- Data clearly shows it to be superior to LMWH when given postoperatively, & probably superior to LMWH given preoperatively
FONDAPARINUX

- Offers possibility of post-op prophylaxis against DVT with same or better efficacy as preop administration of LMWH
- Small but real incidence of wound hematomas (nil if given > 6 hrs post-op); bleeding risk otherwise similar to LMWH
- Avoids problems with administration of drug during regional anesthesia, since can be given after the epidural catheter is pulled
- Approved for treatment of VTE (7.5 mg QD)

Prophylaxis vs TE Disease

- Requires smaller dose than does treatment
- Less risk of bleeding with prophylaxis doses
- Stratified by risk of developing thromboembolic disease
- In surgery patients, pre-op therapy generally more effective than post-op therapy (with one exception)
Primary Risk Factors for VTE

- Major Surgery
  - Leg > Pelvic > Abdominal or Thoracic
- Acute MI
- Major Trauma
- Paralytic Stroke
- Cancer
- Spinal Cord Injury
- Pelvic Fracture

Secondary Risk Factors for VTE

- Congestive Heart Failure
- Previous VTE
- Immobilization
- Obesity
- Chronic Respiratory Failure
- Increasing Age
- Hematological Disorders
- Central Venous Catheter
- Varicose Veins
- Pregnancy
- Estrogen Therapy
- Hospitalization
Prophylaxis vs TE Disease

- **Low Risk** – Minor procedure, otherwise healthy
  - No medications; rapid mobilization

VTE Prophylaxis
Moderate Risk

- **Moderate Risk** – Abdominal surgery, thoracic surgery, Medical patient
  - Multiple medical regimens effective, including:
    - Heparin 5000 units SQ Q 12h
    - Enoxaparin 40 mg SQ QD
    - Dalteparin 5000 units SQ QD
**VTE Prophylaxis**

**High Risk**

- High Risk – Paraplegic, hemiplegic, pelvic surgery, leg surgery
  - Moderate risk therapy ineffective; more clearly needed
    - Enoxaparin 30 mg SQ Q 12h
    - Fondaparinux 2.5 mg SQ QD

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**Direct Thrombin Inhibitors**

- Block active site of thrombin
- Inhibit both clot-bound and free thrombin
- More potent inhibitors than heparin
- All are short-acting, IV infusions
Direct Thrombin Inhibitors

- **Lepirudin (Refludan®)**
  - Hirudin derivative
  - Half life 30-40 minutes
  - Problematic in renal disease
  - Not reversible
  - Approved for Heparin-Induced Thrombocytopenia and Thrombosis

Direct Thrombin Inhibitors

- **Argatroban®**
  - Small molecule active site blocker of thrombin
  - Half life 30-40 minutes
  - Problematic in liver disease
  - Not reversible
  - Approved for Heparin-Induced Thrombocytopenia and Thrombosis & for Acute Coronary Syndromes
Direct Thrombin Inhibitors

- Bivalirudin (Angiomax®)
  - Hirudin derivative
  - Short-acting
  - Not reversible
  - Approved for unstable angina/angioplasty

COUMADIN (warfarin)  
*Mechanism of Action*

- Inhibits Vitamin K dependent carboxylase activity
- Prevents reduction of Vitamin K
- Humans secrete proteins lacking γ-carboxyglutamic acid, which are inactive
- **DOES NOT AFFECT PROTEINS ALREADY SYNTHESIZED**
- Monitor using prothrombin time
- Multiple interactions with other drugs
- Antidote-Vitamin K
Thrombolytic Therapy

- Lyses clot already formed
- Does not discriminate between therapeutic & pathologic thrombosis; therefore
- Markedly increased risk of hemorrhage c/w other antithrombotic therapies
- Only therapy documented to prevent tissue death in acute arterial thrombosis

THROMBOLYTIC THERAPY

- **Streptokinase**
  - Purified from bacteria (Streptococcus)
  - Binds to plasminogen, & complex activates a second plasminogen molecule to plasmin
  - High incidence of allergic reactions
- **Urokinase**
  - Purified from urine initially
  - Recombinant form now available
  - Activates plasminogen directly
- **Tissue plasminogen activator**
  - Made by endothelial cells
  - Increased affinity for fibrin-bound plasminogen ➔ relative fibrin specificity
  - Recombinant form available
  - Activates plasminogen directly
THROMBOLYTIC THERAPY

**Actions**

- Used in myocardial infarction
  - Lyses coronary thrombi
  - Improves/preserves LV function
  - Decreases mortality
  - High rate of reocclusion-esp with TPA
- Lyses hemostatic plugs everywhere
  - Increased incidence of bleeding - esp CNS
  - Lowers plasma fibrinogen
- ? which drug is superior