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 cycloxygenase; irreversibly inhibits the enzyme
- Since platelets have no protein synthetic mechanism, cannot correct defect caused by modification of cycloxygenase
- 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

Diprydamole
- ? 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

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

**Actions**

- 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

- 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
- Lower's plasma fibrinogen
- ? which drug is superior