Hemostasis/Thrombosis IV

Antithrombotic Therapy

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
  - Prasugrel

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

Aspirin

- At low dose (81 mg daily), inhibits thromboxane A2 production
  - Blocks both platelet aggregation & vasoconstriction
- At higher doses (325 mg daily), blocks both thromboxane A2 & prostacyclin (PGI2) production
  - PGI2 inhibits platelet aggregation & causes vasodilation

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
  - Blocks calcium release from dense granules, blocking arachidonic acid production & thereby decreasing thromboxane A2 production
- Decreases platelet aggregation
- Enhances aspirin's effect on platelet aggregation

Glycoprotein IIb/IIIa Inhibitors

- All interfere with fibrinogen-induced platelet aggregation
- 3 classes:
  - Fab fragments (abciximab)
  - Peptide-based antagonists (eptifibatide)
  - Small molecule inhibitors (tirofiban)
- Extremely potent – Platelet count functionally zero
- Drug half-life:
  - Abciximab – 30 minutes
  - Eptifibatide/Tirofiban – 2-2.5 hours

Glycoprotein IIb/IIIa Inhibitors

- Used to block immediate restenosis following cardiac intervention
- Major cause of thrombocytopenia (2-10%)
- Current drugs too potent for long-term use
- Oral agents have not proven successful thus far

ADP Receptor Inhibitors

- Block $P2Y_{12}$ Receptor, inhibiting ADP-induced activation of platelets
- 3 drugs currently approved:
  - Ticlopidine – Rarely used
  - Clopidogrel
  - Prasugrel

ADP Receptor Inhibitors

- All long-acting (half life 7-8 hours, with active metabolites with half life 2-4 days); all inhibit transfused platelets as well as patient's platelets
- No reversing agent

ADP Receptor Inhibitors

- Uses:
  - Unstable angina/Non-ST elevation MI
  - ST elevation MI
  - Percutaneous coronary intervention (in conjunction with aspirin)
  - ? Peripheral vascular disease
  - Stroke

ADP Receptor Inhibitors

- Side effects:
  - Bleeding
    - Esp with surgery
  - Thrombotic thrombocytopenic purpura (esp ticlopidine)
  - Neutropenia (esp ticlopidine)

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

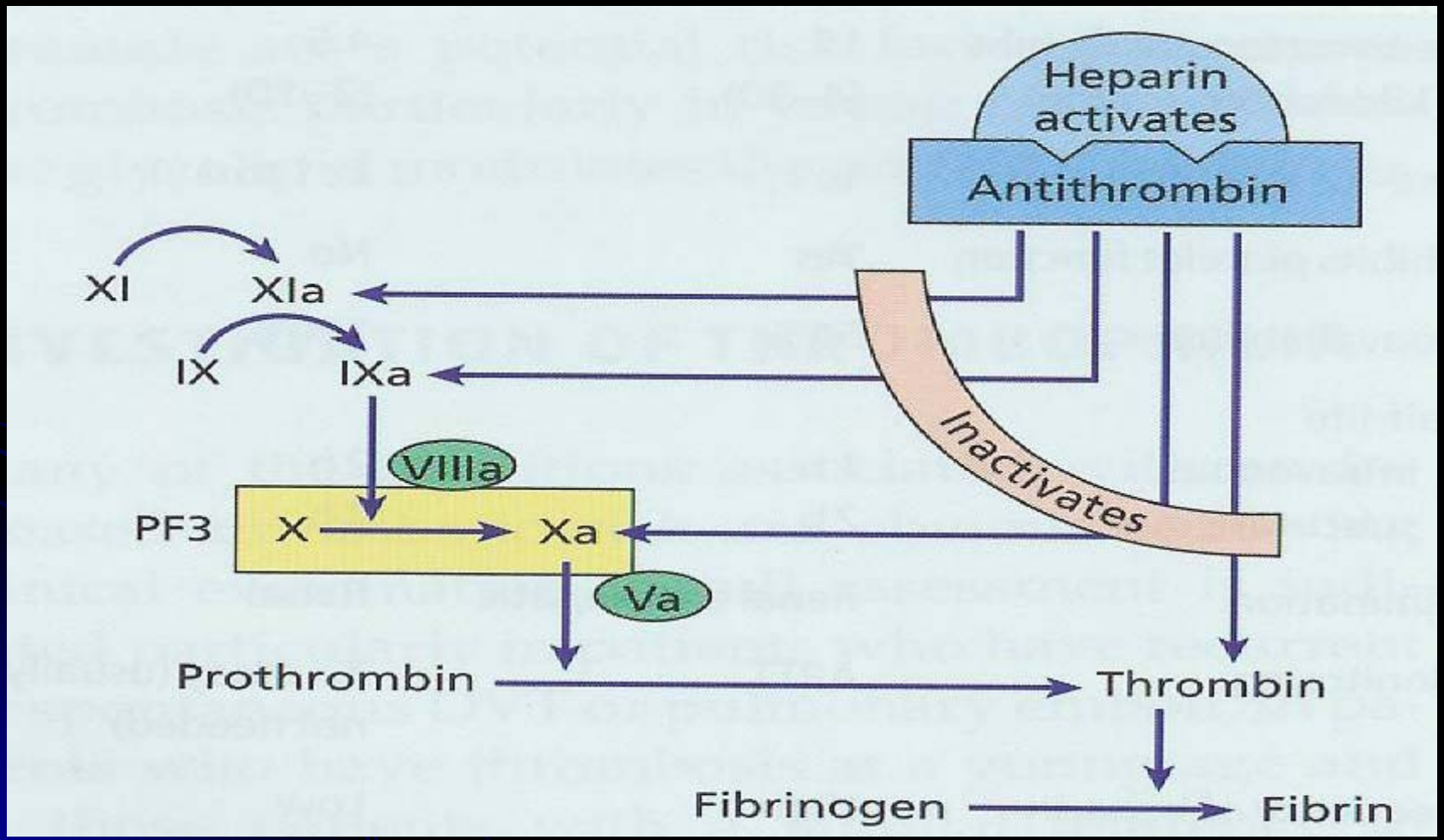
Available Anticoagulants

- 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
  - 4 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

Unfractionated Heparin 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, pregnancy)
- Longer half-life; therefore can be given subcutaneously1-2x/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

Low Molecular Weight Heparins 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 8-12h
    - 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

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

Direct Thrombin Inhibitors

- Desirudin
  - Hirudin derivative (minus 1 sulfate group)
  - Half-life 6-7 hours
  - Approved for DVT prophylaxis in HIT
  - Not yet available

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 compared with 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

Future Agents (Not yet approved)

- Rivaroxaban – Oral Xa inhibitor; in final stages @ FDA now (approved in Europe & Canada)
- Dabigatran – Oral thrombin inhibitor - @ FDA (approved in Europe & Canada)
- Apixaban – Oral factor Xa inhibitor; in final FDA stages now
- Idraparinux – Hyperglycosylated fondaparinux; ½ life 1 week; for extended prophylaxis
- ? Other direct thrombin inhibitors for uses other than HIT
- ? Orally active heparin/LMWH derivatives