Coagulation, Drugs, and the OR

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Coagulation Pathway

Intrinsic pathway (Contact)

Extrinsic pathway (Tissue factor)

X → Xa

Prothrombin → Thrombin

Fibrinogen → Fibrin
Some additional information

- Factors II (prothrombin), VII, IX, and X are vitamin K dependent. (Extrinsic pathway)
  - Vitamin K is cofactor in carboxylation of factor precursors in liver

- Clotting factors are synthesized in the liver except for vWF – which is synthesized by the endothelium of blood vessels.
Heparin – Action

- Heparin acts as cofactor to antithrombin III
  - Heparin-AT III complex primarily inhibits factor Xa and thrombin in 1:4 ratio

- The above reaction goes 1000 to 3000 times faster with heparin.
A small amount (probably LMW heparin) is eliminated unchanged by the kidney. Much of the heparin clearance occurs in the liver, so clearance is reduced in cirrhosis or hepatitis.
Vascular surgery: 5-7000 units loading. Keep ACT > 250 or 2-3000 units every hour

For CPB load with 300 units/kg. 10k units in pump. Adjust if necessary to keep ACT >> 380

Often see tachycardia and/or hypotension on large heparin loading
Heparin Dosing-2

- Often needs more heparin to achieve same effect if patient has been on heparin
  - Antithrombin III level lower in heparinized patients

- May need to give FFP first to boost AT III levels if patient is refractory to heparin
Heparin Antidote

- Can be reversed by protamine sulfate titrated so that 1.3 mg of protamine sulfate is administered for every 100 units of heparin REMAINING in the patient.
  - Excess protamine makes re-heparinization harder
  - Protamine sulfate is also a weak anticoagulant
Protamine Reactions

- Hypotension
  - Histamine release mainly from macrophages in lung tissue
- Pulmonary hypertension
  - Prostaglandin and thromboxane release in lung tissue
- Anaphylactic response
  - Prior exposure to protamine
Heparin-induced Thrombocytopenia

- 2\textsuperscript{nd} most common side effect after bleeding
- Immunologically related
- Occurs in 3-5\% of patients 5 to 10 days after initiation of therapy of standard heparin
- In 1/3 of pts is preceded by thrombosis
- Can be life-threatening even if treated
- Lower incidence in low molecular weight heparin.
Drugs Associated with Thrombocytopenia

- Abciximab
- Acetazolamide
- Allopurinol
- Aminogluthethimide
- Amphotericin B
- Beta-Lactam Antibiotics
- Carbamazepine
- Chlorothiazide
- Cimetidine
- Colchicine
- Desipramine
- Diazepam
- Digoxin
- Disopyramide
- Fluconazole
- Furosemide
- Ganciclovir
- Gold Salts
- Heparin
- Hydrochlorothiazide
- Hydroxychloroquine
- Imipenem-cilastatin
- Interferon
- Isoniazid
- LMWH
- Meclofenamate
- Milrinone
- Morphine
- NSAIDs
- Phenothiazines
- Phenytoin
- Procaainamide
- Quinidine
- Quinine
- Rifabutin
- Rifampin
- Sulfanomides
- Sulfonylureas
- Ticlopidine
- Trimethoprim
- Valproic Acid
- Vancomycin
Heparin and Pregnancy

- Heparin does not cross the placenta, therefore it must be used instead of warfarin in cases of requiring anticoagulant therapy in pregnancy.

- Warfarin crosses the placenta and induces fetal warfarin syndrome.
Low Molecular Weight Heparin

- Has an average mol. wt of 4,500 daltons and 15 monosaccharide units.
- Is isolated from standard heparin
- Is absorbed more uniformly
- Higher bioavailability (greater than 90%)
- Has a longer biological half-life
- Has a more predictable dose-response because it does not bind to plasma proteins, macrophages, or endothelial cells.
Low Molecular Weight Heparin

- Less likely to cause thrombocytopenia
- Can be given SC once or twice daily without monitoring.
- Is cleared unchanged by kidney (Do not use in renal failure!) rather than by mononuclear phagocyte system (RE system) as is for standard heparin.
Warfarin - Action

- Inhibits the synthesis of Vitamin K dependent factors (in order of potency)
  - Factor II
  - Factor X
  - Factor VII
  - Factor IX
Warfarin - Effect

- Takes 8-12 hours before effect is observed
  - That is how long it takes for the four factors to be used up
Warfarin - Antidote

- Vitamin K (oral or parenteral)
  - Takes time before effect of warfarin dissipates.
  - Liver needs to re-synthesize all those factors
- FFP
Warfarin – Administration, Absorption, Biotransformation

- Administered orally
- Biotransformed by the liver
- Completely absorbed – crosses all membranes
  - Crosses GI mucosa
  - Crosses placenta – is teratogenic
  - Is found in breast milk
Warfarin – Drug-Drug Interactions

- Many drug-drug interactions

- The following drugs stimulate the biotransformation of warfarin:
  - Barbiturates
  - Phenytoin
  - Rifampin
  - Alcohol (chronic ingestion)
Warfarin – Drug-Drug Interactions

- The following drugs inhibit warfarin biotransformation
  - Cimetidine (Tagamet)
  - Disulfiram (Antibuse)
  - Large amount of alcohol at one time
  - Amiodarone (Cordarone)
Argatroban

- Direct thrombin inhibitor
- Reversibly binds to thrombin active site
- Does not require antithrombin III
- Eliminated by cP450 system in liver
- Indicated for people unable to tolerate heparin
- No specific antidote for reversal
- Half life 39-51 minutes; full reversal in 4 hours
Argatroban Dosing

- Actually never tested for CPB in humans
- 350 mcg/kg loading dose; 25 mcg/kg/min maintenance
- Monitor ACT as usual
- No adjustment necessary for renal impairment
- Reduce dosing for hepatic failure
Anti-Fibrinolytics

- Aprotinin (Trasylol)
- Aminocaproic Acid (Amicar)
- Tranexamic Acid
Aprotinin

- Serine protease inhibitor (trypsin, plasmin, and kallikrein)
- Inhibits fibrinolysis
- Inhibits platelet activation and aggregation
- Anti-inflammatory
- Rapidly cleared from body; initial half life 0.7 hours
Aprotinin Dosing

- Full Dose: 1 mL test; 200 mL loading; 200 mL in pump; 50 mL/hr maintenance

- Half Dose: 1 mL test; 100 mL loading; 100 mL in pump; 25 mL/hr maintenance

- Some studies show that half dose offers no anti-inflammatory and platelet preservation benefit
Aminocaproic Acid (Amicar)

- Inhibits fibrinolysis by inhibition of plasminogen activator
- Rapidly cleared in urine
- 5-10 gm before and after CPB; 5-10 gm in pump
- 5 gm load; 1 gm/hr maintenance
Anti-Platelet Therapy

- Oral Anti-platelet Therapy
  - Aspirin
  - Ticlopidine (Ticlid)
  - Clopidogrel (Plavix)

- IV Anti-platelet Therapy
  - Abciximab (Reopro)
  - Tirofiban (Aggrastat)
  - Eptifibatide (Integrilin)
Aspirin

- Cyclooxygenase (Cox$_{1, 2}$) inhibitor, preventing production of prostaglandins and thromboxane A$_2$
- Permanently inactivates Cox
- Inhibits platelet aggregation
Clopidogrel (Plavix) / Ticlopidine (Ticlid)

- Platelet ADP receptor antagonists
  - Inhibit platelet aggregation/degranulation
- Plavix widely used long term post stenting or CVA prevention
- Hangs around a long time. Greatly increases bleeding.
- This is the drug that scares cardiac surgeons the most
- Almost always see aproninin used in CPB
Reopro/Integrilin/Aggrastat

- GPIIb/IIIa antagonists
- Most potent anti-platelet drugs available
- Used only in cath lab
- Prevents platelet aggregation
- Reopro with shortest half life 30 minutes
- Encounter these drugs in cath lab crashes
- Again, apronininin may be helpful
Coagulation Studies

- ACT
- Platelet Count
- Platelet Function Test
- aPTT
- PT/INR
- Fibrinogen Count
- Fibrin Split Products
Activated Coagulation Time

- Celite ACT
  - Normal is 100-170 seconds
  - Black top tube
  - Aprotinin prolongs normal ACT

- Kaolin ACT
  - Normal is 90-150 seconds
  - Gold top tube
  - Aprotinin independent

ACT > 380 for CPB; ACT > 300 for OPCAB
Platelet Count

- Platelet count does not tell you platelet function
  - All platelets get “stupid” after bypass
  - Need to do platelet function test if you really want to know
  - Most of the time unnecessary
PT / INR / aPTT

- PT/INR measures Vitamin K dependent pathway, mainly factor VII
  - Use INR for standardization
  - Coumadin therapy
  - Hi dose heparin

- aPTT
  - Heparin therapy
  - Hi dose coumadin
  - LMWH does not increase aPTT reliably
    - LMWH mainly inactivates factor Xa, but not thrombin
Fibrinogen / Fibrin Split products

- DIC panel
  - Fibrinogen down
  - Fibrin Split products (d-dimer) up

- Whole different topic
Additional information

- www.labtestsonline.org
- www.anaesthetist.com/icu/organs/blood/c_index.htm