

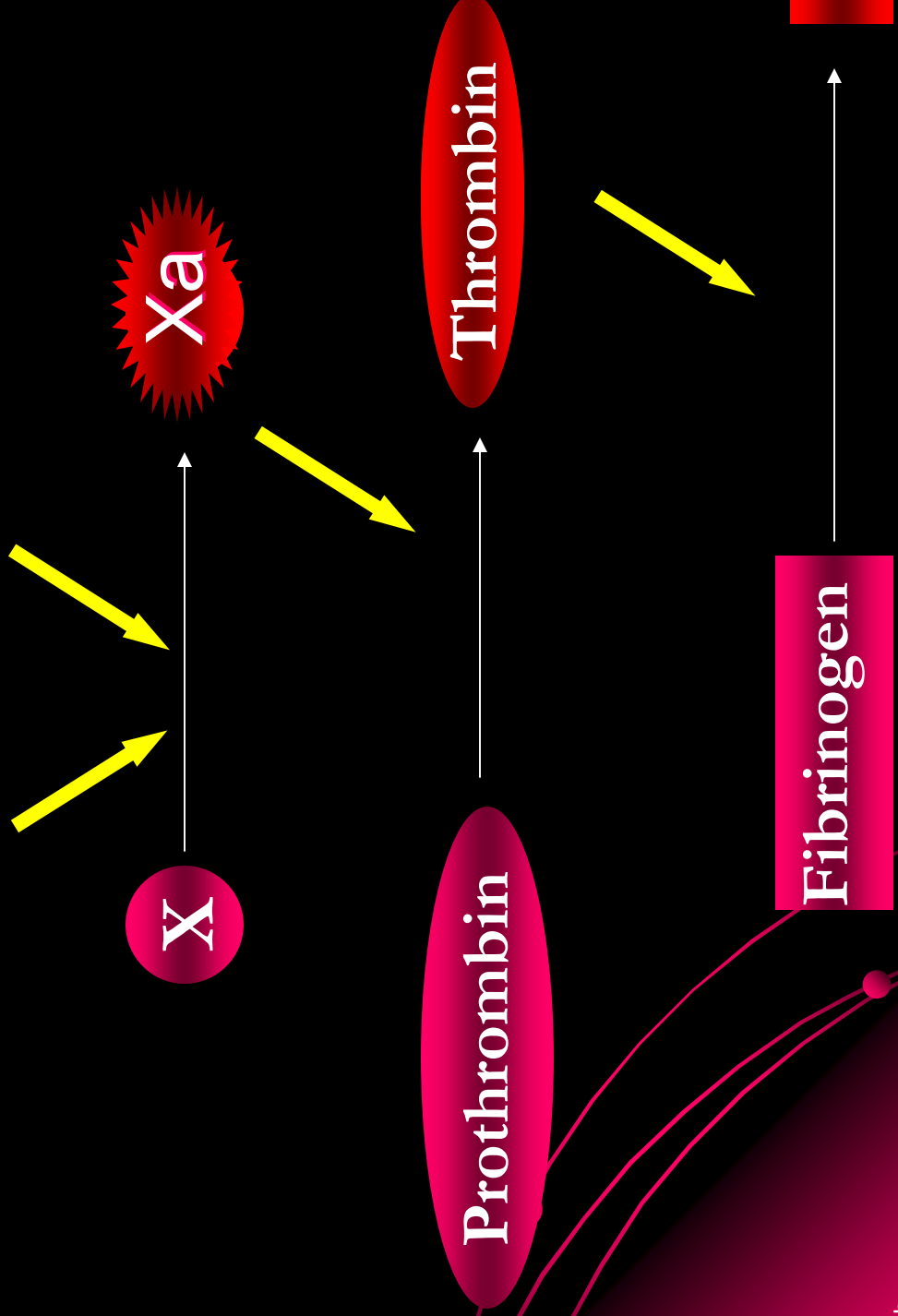
Coagulation, Drugs, and the OR

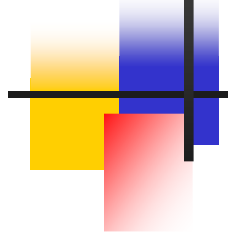
October 7, 2006
Jeffrey Chen, MD

Coagulation Pathway

Intrinsic pathway
(Contact)

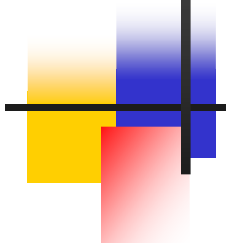
Extrinsic pathway
(Tissue factor)





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.





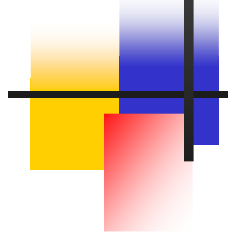
Heparin – Action

- 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.



Heparin – Elimination

- Much of the heparin clearance occurs in the liver, so clearance is reduced in cirrhosis or hepatitis.
- A small amount (probably LMW heparin) is eliminated unchanged by the kidney.



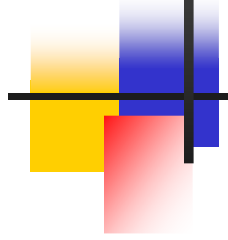
Heparin Dosing-1

- 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



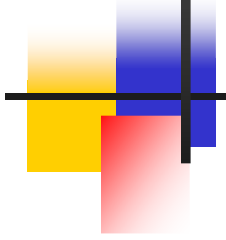
Heparin Dosing-2

- 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 reheparinization 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

- 2nd 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	Imipenem-cilastatin
Acetazolamide	Interferon
Allopurinol	Isoniazid
Aminoglutethimide	LMWH
Amphotericin B	Meclofenamate
Beta-Lactam Antibiotics	Milrinone
Carbamazepine	Morphine
Chlorothiazide	NSAIDs
Cimetidine	Phenothiazines
Colchicine	Phenytoin
Desipramine	Procainamide
Diazepam	Quinidine
Digitoxin	Quinine
Disopyramide	Rifabutin
Fluconazole	Rifampin
Furosemide	Sulfanomides
Ganciclovir	Sulfonyleureas
Gold Salts	Ticlopidine
Heparin	Trimethoprim
Hydrochlorothiazide	Valproic Acid
Hydroxychloroquine	Vancomycin



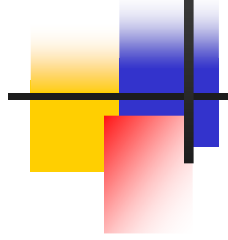
Heparin and Pregnancy

- 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 (RES 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



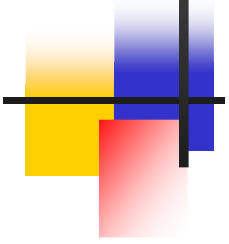
Warfarin – Administration, Absorption, Biotransformation

- 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



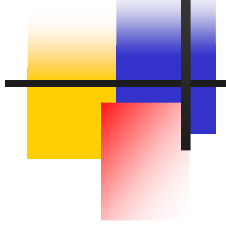
Anti-Platelet Therapy

- 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 A₂
- 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



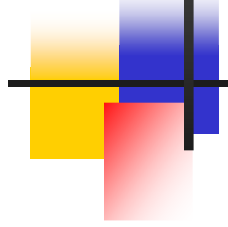
Reopro/Integrilin/Aggrastat

- 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, aproninin 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



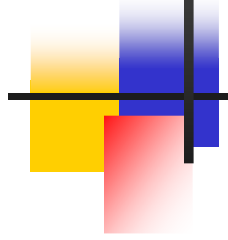
Platelet Count

- 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

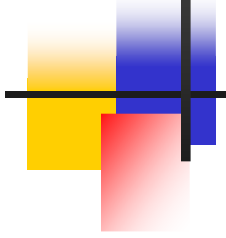
- PT/INR measures Vitamin K dependent pathway, mainly factor VII
 - Use INR for standardization
 - Coumadin therapy
 - Hi dose heparin
- aPTT
 - Heparin therapy
 - Hi dose coumadin
 - LMWH does not increase aPTT reliably
 - LMWH mainly inactivates factor Xa, but not thrombin



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