

The Amazing World of Coagulation

Christopher F. Sirridge M.D.

The Amazing World of Coagulation

- 99% of our existence we need fluid flow of blood = no clots.
- 0.01% time we need to clot so as to not hemorrhage.

The Amazing World of Coagulation

However:

- The number one pathophysiologic cause of death in the world is hypercoagulability.
- *WOW!!* 0.01% of our time on this earth is the main cause of death.

Why are Clots the Number one Killer

- 93% of all acute myocardial infarctions are fresh clot.
- 91% of all acute CVA's are fresh clot.
- 100% of all pulmonary emboli are fresh clot.

Clots Are No Fun When They Don't Kill You

- Neurological deficits – some severe.
- Pulmonary hypertension – dyspnea.
- Heart failure.
- Post-phlebotic syndrome.

Clots Are No Fun When They Don't Kill You

- Venous/lymph edema.
- Loss of bowel.
- Acute renal failure.
- Congestive heart failure.

Clots Are No Fun When They Don't Kill You

- Congestive Hepatomegaly.
- Medication necessities.
- Many others.

Four Basic Components of our Coagulation System

- Blood vessels.
- Platelets.
- Coagulation cascade.
- Fibrinolytic response.

Component #1 – Blood Vessel

- Collagen.
- Muscle wall.
- Free or obstructive flow.
- Either a "Good" witch or a "Bad" witch.

Component #2 - Platelets

- Blood cells that form the primary plug.
- Interact with coagulation cascade.
- Recruit red cells.

Component #2 - Platelets

- NL or ABNL numbers, NL or ABNL function.
- Argue, "*lowly platelet*" is the BMOC – "*Big Man On Clot*".

Component #3 – Coagulation Cascade

- Plasma proteins in symphonic cadence that produce a clot - Good or Bad.
- Individual diseases of each protein.
- "BIG Dudes" and "Little Duddettes"

Component #3 – Coagulation Cascade

- Target of multiple medications.
- Subject of many lab tests.
- Vitally important in seriously ill patients.

Component #3 – Coagulation Cascade

- Although often poorly understood, absolutely vital to the diagnostic therapeutic management of critically ill patients.

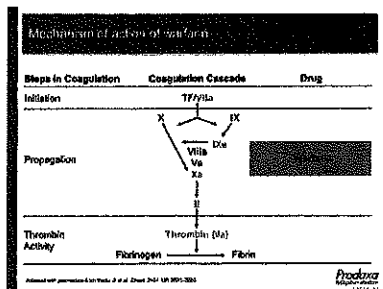
Component #4 – Fibrinolytic System

- What gets clotted – must get unclotted.
- Internal, Intrinsic Vascular “Liquid Plummer”.

Component #4 – Fibrinolytic System

- Vital in D.I.C. (Disseminated Intravascular Coagulation).
- TPA, Streptokinase, Alteplase, Amicar are Active!!

Coagulation Cascade



Coagulation Cascade

- Platelets active throughout cascade.
- Calcium (CA++) is active everywhere.
- Occurs in a microsecond.

Coagulation Cascade

- "BIG Dudes" are:
 - Factor VII A
 - Factor XA
 - Thrombin (IIA)
 - Fibrinogen (I)

Coagulation Cascade

- All medications, diseases and laboratory tests defining blood clotting are based on this cascade.
- A simple but complete working knowledge of this cascade makes a world of difference.

Medications

Handy, dandy list of often used medications to alter the clotting process.

- Anti-platelet drugs - ASA, Plavix, (cyclo-oxygenase inhibition, ADP, IIb, IIa, Effient, Persantine, Intergrelin).

Medications

- Systemic UFH - (unfractionated heparin), LMWH, Fondaparinux, Riveroxaban, Argatroban, Dabigatran. Inhibitors of any coagulation factor, Xa inhibitors, Thrombin inhibitors.

Medications

- Fibrinolytic inhibitors of any stage of fibrinolysis, or enhancers of fibrinolysis.
- –Amicar (Epsilon Amino Caproic Acid).

Medications

- TPA (Tissue Plasminogen Activator).
- Streptokinase.
- Alteplase.

Platelet Inhibitors

- Stop aggregation.
- Stop degranulation.
- Stop migration.

Platelet Inhibitors

- Platelets live 8 - 10 days.
- All but Integrelin are irreversible during life of the platelet.

All but Integrelin are dosed daily to poison the newly released platelet

- To get reasonably NL platelets – stop anti-platelet med for 5 days.
- For *“Perfect Platelet”* 10 days.
- ABNL bleeding is usually superficial/mucosal (Epistaxis, bruising, GI oozes).

Systemic Anticoagulants

- Inhibit the clotting cascade.
- Explosion of new options.

Systemic Anticoagulants

- How do they work, how do we measure them, can we reverse them?
- *“Special Niches”* for these drugs.

Coumadin (Warfarin) (Rat Poison)

- Vitamin K antagonist.
- Decrease amount of vitamin K dependent clotting factors (2,7,9,10).

Coumadin Handy Info

- Generic, cheap, require frequent INR testing – even with Q 4-6 wk INR's Coumadin is only therapeutic 50% of the time.

More Coumadin Handy Info...

- There is no antidote.
- Vitamin K takes days to reduce INR.
- Treatment for bleeding is fresh frozen plasma, cryoprecipitate occasionally activated factor VIIA.

More Coumadin Handy Info...

- Hematologist and blood products can't stop an atomic bleed. GI doc's, surgeons and interventional radiologist have to do their part.

More Coumadin Handy Info...

- Hematologist can modify bleeding and buy time – but most serious bleeds are an open vessel or plexus of vessels.

Final Coumadin Thoughts

- Brand name is more reliable than generic.
- Generic Coumadin initiates hair loss/thinning.

Final Coumadin Thoughts

- Unchallenged as an oral anticoagulant for 56 years!!!
- What is the correct INR for the individual patient with a unique disease? Expert opinions vary significantly.

Final Coumadin Thoughts

- Lovenox or other product "Bridges" are unpopular with patients.
- Frequent INR testing is tedious and expensive even with F5 immediate results.

UFH (Unfractionated Heparin)

- Intravenous or sub-Q usage.
- Mainstay of systemic anticoagulation for decades.

UFH (Unfractionated Heparin)

- APTT (activated partial thromboplastin time) or UFH specific anti XA are monitoring test of choice.
- Treatment of pathologic clotting or prophylaxis.

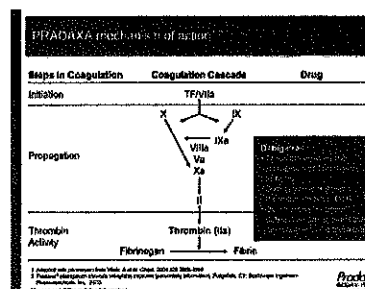
UFH (Unfractionated Heparin)

- Short ½ life 30-60 minutes IV 60-90 minutes sub-q.
- Specific and direct antidote-protamine.
- Sulfate (1 mg/100 units UFH) up to 100 mg.

UFH (Unfractionated Heparin)

- 1:1 stoichiometric bond with anti-thrombin III- and partially inactivates IIA (thrombin).

Coagulation Cascade



Handy UFH Info...

- 5-10% incidence of Thrombocytopenia.
- 2-3% "HIT" Heparin Induced Thrombocytopenia. Serious and potentially fatal complication.
 - Draw "HIT" antibody.
 - If +, then anticoagulation w/ Arixtra, Argatroban.

Handy UFH Info...

- Prophylactic ally UFH should be used Q 8 hours.
 - Other than near term obstetrics.UFH prophylaxis is assuming dinosaur status.

Handy UFH Info...

- CHEAP...it does require frequent monitoring.

LMWH (Low Molecular Weight Heparin)

- 25 amino acids compared to 26 UFH
 - Less Antigenic
 - Longer ½ life, sub-q about 4-6 hours.
 - Getting cost reasonable.

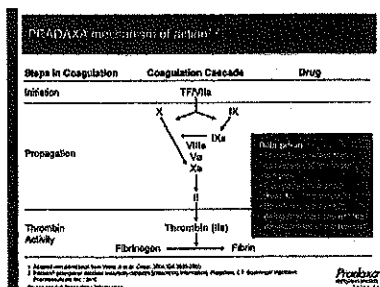
LMWH (Low Molecular Weight Heparin)

- 1-2% Thrombocytopenia and 1% "HIT".
- Measured with LMWH specific anti-XA.
- Once/day prophylaxis, except for hips/knees Q 12 hrs because of nature of surgery.

LMWH (Low Molecular Weight Heparin)

- Immediately absorbed, therapeutic 20-30 minutes.
- Procedural "bridging" for Coumadin patients.
- Can be given once or twice a day for full therapeutic intervention.

Coagulation Cascade



Dabigatran

- New "Kid" on the block.
- FDA approved for non-valvular A-Fib.
- Used in UK, Europe, Canada, Australia, "Kiwis" for over 5 yrs for all hypercoagulability.

Dabigatran

- ½ life for 12 hrs w/ good renal function.
- Twice a day dosing.
- 2nd fastest growing med in U.S. history
500,000 new scripts in 2011.

Dabigatran

- No standard lab testing required.
- Therapeutic in 60-90 minutes.
- No LMWH "Bridges".

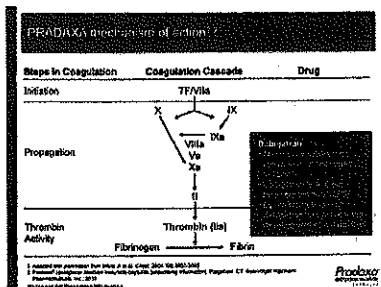
Dabigatran

- No vitamin K restrictions.
- No antibiotic/diet restrictions.
- 90% w/I therapeutic range rely study.

Dabigatran

- If a need arises to evaluate Pradaxa, APTT, Thrombin time are sufficient.

Dabigatran



Handy Dabigatran Info...

- No direct antidote.
- Always be aware of renal function.
- 5% incidence of GERD.

Handy Dabigatran Info...

- Slight increase, GI bleeds in pts > 75 yrs.
- Fresh frozen plasma, cryoprecipitate, or activated VIIA Rx are antidotes of choice, if necessary.

Handy Dabigatran Info...

- Dialyze if you must.
- Check APTT or thrombin time if you must know basic level of anticoagulation.

Xeralto (Riveroxaban)

- Anti-XA inhibitor (oral).
- FDA indications for prophylaxis for hip/knee replacements, non valvular atrial fibrillation.

Xeralto (Riveroxaban)

- 10 mg a day.
- ½ life is 5-9 hrs.
- Renal excretion – can't use GFR < 30 mL/min.

Xeralto (Riveroxaban)

- Superior to Lovenox for DVT prophylaxis but study flawed.
- No specific antidote.
- FFP, cryoprecipitate.

Xeralto (Riveroxaban)

- PGPCyp3a4 drug interaction...St John's Wort.