Lecture 10 Outline

Antithrombotic Therapies

1. Anticoagulant Therapy — “Old Drugs”
   1. General Information:
   2. Heparin
      1. Description
         1. Very heterogeneous molecule composed of repeating disaccharide units
         2. Molecules have different lengths
         3. From bovine lung or porcine intestine
         4. Very negatively charged
         5. Mean molecular weight = 12,000-15,000 daltons
      2. Given by IV; t 1/2 = 1-2 hours = half life
      3. Has long chains, which enable its action, although primarily a pentasaccharide sequence that is active
      4. Heparin acts on on preformed thrombin; given when have had a thrombotic event to stop clotting process; also given to anticoagulant a patient who is going to have surgery or procedure when can trigger activation of clotting mechanism
      5. Good, but can have complications
      6. Heparin also binds to other plasma proteins; therefore, response not always predictable — increased plasma proteins can bind heparin, so has decreased anticoagulant response
      7. Because of different response, must monitor
      8. Use PTT; must achieve certain range, equivalent to 0.3—0.7 anit-Xa units
      9. Anti-Xa activity — specific for amount of heparin in patient sample
      10. Give protamine sulfate to patient to neutralize heparin in their body (reversible)
   3. LMWH (Enoxaparin)
   4. Fondaparinux (newer)
      1. Similar to heparin, but is a synthetic version; it is the active pentasaccharide sequence in heparin that binds to AT.
      2. Selectively inhibits Xa after binding to AT III with high affinity
      3. Because 5 pentasaccharides, too short to bridge antithrombin to thrombin; therefore, doesn’t inhibit thrombin
      4. T 1/2 = 15 hours —> give once daily
      5. Predictable response, so lab monitoring only in certain situations
      6. Low risk of HIT
      7. Excreted by kidneys
   5. Oral Anticoagulants — warfarin (Coumadin)
2. Anticoagulant Therapy — “New Drugs”
   1. General information: Target specific; inhibits specific factors
   2. Direct thrombin (IIa) inhibitors
      1. Include hirudin, bivalirudin, argatroban, dabigatran
      2. Hirudin — most potent natural inhibitor of thrombin
         1. Good for plastic or reconstructive surgery
         2. Leech bites… has hirudin which inhibits thrombin. They are still used today for therapy.
      3. Bivalirudin (Angiomax) = synthetic derivative of hirudin
         1. Specific, direct, reversible thrombin inhibitor which is independent of AT III (reversible means that as thrombin slowly cleaves the bivalirudin-thrombin bonds, thrombin recovers its active site functions)
         2. Synthetic derivative of hirudin
         3. 20 amino acids
         4. Binds to both free and clot-bound thrombin
         5. No antidote; t 1/2 = 25 minutes (half life)
         6. Don’t form antibodies
         7. Monitored with PTT
         8. Used in patients undergoing angioplasty (given by IV)
      4. Argatroban = synthetic
         1. Used in cardiac surgery if heparin cannot be used (e.g. HIT patients)[CABG = coronary artery bypass grafting] (given by IV)
         2. Synthetic molecule; highly selective direct thrombin inhibitor
         3. Binds to both free and clot-bound thrombin
         4. No reversal agen (i.e. antidote) if you give too much; t 1/2 = 50 minutes (half life)
         5. Hepatic excretion — good for those with renal failure
         6. No reports of antibodies
         7. PTT to monitior
      5. Dabigatran
   3. Direct Xa Inhibitors: unlike LMWH and fondaparinux, these drugs inhibit Xa without the need for AT — Apixaban and rivaroxaban
      1. Oral, reversible specific Xa inhibitors (reversible means that after the Xa binds and slowly cleaves the drug, Xa will recover its active site functions)
      2. Inhibit free and fibrin-bound Xa
      3. Rapid onset of action (peak activity in 1-3 hours)
      4. T 1/2 = 9-10 hours
      5. Predictable pharmacokinetics — no need for monitoring
      6. No effect on platelet function
      7. Apixaban excreted primarily via feces; rivaroxaban eliminated primarily via kidneys
   4. Problems/ concerns with all these anticoagulant drugs, IIa and Xa inhibitors
      1. Safety
      2. Efficacy (ability to produce desired result)
      3. Risk of bleeding
      4. Lack of antidote
      5. Other side effects
      6. Cost
3. Thrombolytic Therapy
   1. Thrombolytic drugs are those that dissolve a clot which has already formed (e.g. when a person has had a heart attack or stroke)
   2. According to the American Heart Association, you have a better chance of surviving and recovering from a heart attack if you receive a thrombolytic drug within 12 hours after the heart attack starts, but ideally yo should receive thrombolytic medications within the first 90 minutes after the even occurs. This is because thrombi have extensive polymerization that makes thrombin more resistant to breakdown.
   3. Generally these drugs are administered directly to the site of the thrombus.
4. Anti-Platelet Drugs


   3. Two oral drugs
      1. Aspirin:
      2. Plavix:
   4. COX inhibitor
   5. ADP receptor blockers

(Thienopyridines are a class of ADP receptor/P2Y12 inhibitors used for their ani-platelet activity)

* + 1. Group of drugs called thienopyridines
    2. Work by binding to and blocking the platelet ADP receptor sites
    3. Given orally
    4. Three drugs
       1. Ticlopidine
       2. Prasugrel
       3. Clopidogrel (Plavix)
  1. GPIIb/IIIa inhibitors
     1. These bind to the intact platelet GPIIb/IIIa receptor —> inhibit platelet aggregation
     2. Given by IV
     3. Abciximab (Reopro), tirofiban (Agggrastat), and eptifibatide (Integrelin)
     4. Inhibition by these is from 4-48 hours