Oral Anticoagulant Drugs

- Spoiled sweet clover caused hemorrhage in cattle (1930s).
- Substance identified as bishydroxycoumarin.
- Initially used as rodenticides, still very effective, more than strychnine.
- Warfarin was introduced as an antithrombotic agent in the 1950s.
Oral Anticoagulant Drugs

**Warfarin:**

- Is one of the most commonly prescribed drugs, usually underprescribed.
- 100% bioavailability, peaks after one hour.
- 99% bound to plasma proteins, leading to small volume of distribution and long half life (36 hr). Does not cross BBB, but crosses the placenta.
- Hydroxylated in the liver.
- Present in two enantiomorphs.
Oral Anticoagulant Drugs

Mechanism of Action:

Act in the liver, not in the circulation.

Structure is similar to vitamin K.

- Block the γ-carboxylation which is a final synthetic step that transforms a common precursor into various factors: prothrombin, VII, IX, and X as well as the endogenous anticoagulant proteins C and S.

- This blockade results in incomplete coagulation factor molecules that are biologically inactive.
Oral Anticoagulant Drugs

Mechanism of Action:

The protein carboxylation reaction is coupled to the oxidation of vitamin K.

- The vitamin must then be reduced to reactivate it.
- Therefore, warfarin prevents reductive metabolism of the inactive vitamin K epoxide back to its active hydroquinone form.
Descarboxy-prothrombin

Prothrombin

\[ \text{CO}_2 \quad \text{Carboxylase} \quad \text{CO}_2 \]

\[ \text{Warfarin} \]


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Warfarin

Onset of Action:

- Time to maximal effect depends on factor degradation half-lives in the circulation. VII=6, IX=24, X= 40 and II=60.

- Action starts after about 48 hrs, i.e. after elimination of most of the factors in the circulation.

- Effect results from a balance between partially inhibited synthesis and unaltered degradation of the four vitamin K dependent clotting factors.
Warfarin

- **Administration and Dosage:**
  - Treatment is initiated with small doses of 5-10mg, not large loading doses.
  - Warfarin resistance seen in cancer patients.
  - Response monitored by Prothrombin Time.

- **International Normalized Ratio (INR) =**
  - Patient PT / Mean of normal PT for the lab.
Warfarin

Toxicity:

- Bleeding.
- Teratogenicity.
- Cutaneous necrosis, infarction of breast, fatty tissues, intestine and extremities. This is due to inhibition of Protein C and S, especially in patients genetically deficient in them.
<table>
<thead>
<tr>
<th>Level of Causation</th>
<th>Anti-infectives</th>
<th>Cardiovascular Drugs</th>
<th>Analgesics, Anti-inflammatories, and Immunologics</th>
<th>CNS Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Highly Probable</td>
<td>Ciprofloxacin, Cotrimoxazole, Erythromycin, Fluconazole, Isoniazid (600 mg/d)</td>
<td>Amiodarone, Clofibrate, Diltaizem, Fenofibrate, Propafenone, Propranolol, Sulfipyrazone (biphasic with later inhibition)</td>
<td>Phenylbutazone, Piroxicam</td>
<td>Alcohol (if concomitant liver disease), Citalopram, Entacapone, Sertraline</td>
</tr>
<tr>
<td>II Probable</td>
<td>Amoxicillin/clavulanate, Azithromycin, Clarithromycin, Itraconazole, Levofloxacin, Ritonavir, Tetracycline</td>
<td>Fluvastatin, Quinidine, Ropinirole, Simvastatin</td>
<td>Acetaminophen, Acetylsalicylic acid, Celecoxib, Dextropropoxyphene, Interferon, Tamandol</td>
<td>Disulfiram, Choral hydrate, Fluvoxamine, Phenytin (biphasic with later inhibition)</td>
</tr>
<tr>
<td>III Possible</td>
<td>Amoxicillin, Amoxicillin/claranexamic rinse, Clarithromycin, Ceftriaxone, Miconazole topical gel193, Natuldeic acid, Norfloxacin, Ofloxacin, Saquinavir, Telbinafine</td>
<td>Amiodarone-induced toxicosis, Disopyramide, Gemfibrozil, Metolazone</td>
<td>Celecoxib, Indomethacin, Leflunomide, Propoxyphene, Rofecoxib, Sulindac, Tolmetin</td>
<td>Felbamate, Topical salicylates</td>
</tr>
<tr>
<td>IV Highly Improbable</td>
<td>Cefamandole, Cefazolin, Sulfisoxazole</td>
<td>Bezafibrate, Heparin, Levamisole, Methylprednisolone, Nabumetone</td>
<td>Fluoxetine/diazepam, Quetiapine</td>
<td></td>
</tr>
</tbody>
</table>

### Inhibition

<table>
<thead>
<tr>
<th>Level of Causation</th>
<th>Anti-infectives</th>
<th>Cardiovascular Drugs</th>
<th>Analgesics, Anti-inflammatories, and Immunologics</th>
<th>CNS Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Highly Probable</td>
<td>Griseofulvin, Nafcilin, Ribavirin, Rifampin</td>
<td>Cholestyramine, Mesalamine</td>
<td>Barbiturates, Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>II Probable</td>
<td>Dicloxacillin, Ritonavir</td>
<td>Bosentan, Azathioprine</td>
<td>Chloroalzepoxide</td>
<td></td>
</tr>
<tr>
<td>III Possible</td>
<td>Terbinafine, Telmisan, Sulfasalazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV Highly Improbable</td>
<td>Cloxacillin, Nafcilin/dicloxacillin, Teicoplanin</td>
<td>Furosemide, Propofol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Source: Adapted with permission from reference 30.*
Warfarin

Reversal of Action:

- Vitamin K.
- Fresh-frozen plasma.
- Prothrombin complex concentrates.
- Recombinant factor VII.
Fibrinolytic Agnets

- These drugs rapidly lyse thrombi by catalyzing the formation of the serine protease Plasmin from its precursor zymogen, Plasminogen.
- They create a generalized lytic state.
- Aspirin will be still required.
Fibrinolytic Agents

Streptokinase:

- Protein synthesized by *Streptococcus*.
- Binds with the proactivator plasminogen in plasma to activate it.
- Not fibrin-specific → Bleeding.
- Highly antigenic:
  - Can cause allergic reactions.
  - Can result in inactivation of the drug.
- Early administration is important.
Fibrinolytic Agents

Urokinase:

- Is a human enzyme synthesized by the kidneys.
- Directly converts plasminogen into plasmin.
- Not antigenic.
- Expensive.
Fibrinolytic Agents

Anistreplase (Anisoylated Plasminogen Streptokinase Activator Complex, ASPAC):

- Deacylated at fibrin surface $\rightarrow$ Active complex released.
- More active and selective.
- Long action, $t^{1/2} \rightarrow 6h$
Fibrinolytic Agents

- **Tissue-type Plasminogen Activators (t-PA):**
  - Ateplase
  - Reteplase
  - Tenecteplase

- Synthesized by the endothelial cells, also recombinant.
- Bind to fibrin and activate plasminogen at the fibrin surface.
- Action less affected by age of thrombus.
- Specific action — within the thrombus, avoids systemic activation.
- Short action $t^{\frac{1}{2}} = 8$ min.
- Given by infusion over 1-3 hours.
- Very Expensive.
Fibrinolytic Agents

Indications:

- Pulmonary embolism with hemodynamic instability.
- Deep venous thrombosis.
- Ascending thrombophlebitis.
- Acute myocardial infarction.
Antiplatelet Drugs

Platelet Regulators:

- Agents generated outside platelets and interact with membrane receptors: Catecholamines, collagen, thrombin, and prostacyclin.

- Agents generated inside and interact with membrane receptors: ADP, PGD2, PGE2 and serotonin.

- Agents generated within and interact within platelets: TXA2, cAMP, cGMP and calcium.
Platelet adhesion and aggregation

- GPIa/IIa and GPIb are platelet receptors that bind to collagen and von Willebrand factor (vWF), causing platelets to adhere to the subendothelium of a damaged blood vessel.

- P2Y1 and P2Y12 are receptors for ADP; when stimulated by agonists, these receptors activate the fibrinogen-binding protein GPIIb/IIIa and cyclooxygenase-1 (COX-1) to promote platelet aggregation and secretion.
Platelet adhesion and aggregation

- PAR1 and PAR4 are protease-activated receptors that respond to thrombin (IIa).

- Thromboxane A2 (TxA2) is the major product of COX-1 involved in platelet activation.

- Prostaglandin I2 (prostacyclin, PGI2), synthesized by endothelial cells, inhibits platelet activation.
Sites of action of antiplatelet drugs.

- **Aspirin** inhibits thromboxane A2 (TXA2) synthesis by irreversibly acetyling cyclooxygenase-1 (COX-1). Reduced TXA2 release attenuates platelet activation and recruitment to the site of vascular injury.

- **Ticlopidine, clopidogrel, and prasugrel** irreversibly block P2Y12, a key ADP receptor on the platelet surface; cangrelor and ticagrelor are reversible inhibitors of P2Y12.
Sites of action of antiplatelet drugs.

- Abciximab, eptifibatide, and tirofiban inhibit the final common pathway of platelet aggregation by blocking fibrinogen and von Willebrand factor (vWF) from binding to activated glycoprotein (GP) IIb/IIIa.

- SCH530348 and E5555 inhibit thrombin-mediated platelet activation by targeting protease-activated receptor-1 (PAR-1), the major thrombin receptor on platelets.
Antiplatelet Drugs

- **Aspirin = Acetyl Salicylic Acid**
  - Irreversible acetylation of COX in platelets.

  Platelets do not have DNA or RNA, so aspirin causes permanent inhibition of platelets’ COX (half-life 7-10 days).

  Endothelium can synthesize new COX, so PGI2 production is not affected.

- **Dose:** 80 — 325 mg.
Antiplatelet Drugs

- **Clopidogrel (Plavix).**
  - Irreversibly block ADP receptors on platelets.
  - Useful in TIAs, completed stroke, unstable angina and after placement of coronary stents.
  - Useful for patients who cannot tolerate aspirin.
  - Can cause leukopenia, GI irritation and skin rash.

- **Ticlopidine (Ticlid).**
Antiplatelet Drugs

- **Abciximab.**
  - C7E3 monoclonal antibody of the glycoprotein IIb/IIIa receptor complex.

- **Eptifibatide.**
  - Synthetic peptide.

- **Tirofiban.**
  - All inhibit the platelet glycoprotein IIb/IIIa complex, which works as a receptor mainly for fibrinogen and vitronectin as well as for fibronectin and von Willebrand factor.
Antiplatelet Drugs

Dipyridamole
Cilostazole

Vasodilator.

- Inhibit adenosine uptake and phosphodiesterase enzyme $\rightarrow \uparrow c$ AMP in platelets and elsewhere.
Antiplatelet Drugs

Dazoxiben:
Inhibits TX synthetase enzyme.

Sulotroban:
Inhibits TXA2 receptor.

Anagrelide:
Reduces platelet production by decreasing megakaryocyte maturation.

Lipid Lowering Agents
Hemostatic Agents

- Whole Blood
- Fresh Frozen Plasma
- Plasma fractions.
- Vitamin K.
Table 34-3. Therapeutic products for the treatment of coagulation disorders.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Deficiency State</th>
<th>Hemostatic Levels</th>
<th>Half-Life of Infused Factor</th>
<th>Replacement Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hypofibrinogenemia</td>
<td>1 g/dL</td>
<td>4 days</td>
<td>Cryoprecipitate FFP</td>
</tr>
<tr>
<td>II</td>
<td>Prothrombin deficiency</td>
<td>30–40%</td>
<td>3 days</td>
<td>Prothrombin complex concentrates (intermediate purity factor IX concentrates)</td>
</tr>
<tr>
<td>V</td>
<td>Factor V deficiency</td>
<td>20%</td>
<td>1 day</td>
<td>FFP</td>
</tr>
<tr>
<td>VII</td>
<td>Factor VII deficiency</td>
<td>30%</td>
<td>4–6 hours</td>
<td>FFP Prothrombin complex concentrates (intermediate purity factor IX concentrates) Recombinant factor VIIa</td>
</tr>
<tr>
<td>VIII</td>
<td>Hemophilia A</td>
<td>30–50% 100% for major bleeding or trauma</td>
<td>12 hours</td>
<td>Recombinant factor VIII products Plasma-derived high purity concentrates Cryoprecipitate¹ Some patients with mild deficiency will respond to DDAVP</td>
</tr>
<tr>
<td>IX</td>
<td>Hemophilia B Christmas disease</td>
<td>30–50% 100% for major bleeding or trauma</td>
<td>24 hours</td>
<td>Recombinant factor IX products Plasma-derived high purity concentrates</td>
</tr>
<tr>
<td>X</td>
<td>Stuart-Prower defect</td>
<td>25%</td>
<td>36 hours</td>
<td>FFP Prothrombin complex concentrates</td>
</tr>
<tr>
<td>XI</td>
<td>Hemophilia C</td>
<td>30–50%</td>
<td>3 days</td>
<td>FFP</td>
</tr>
<tr>
<td>XII</td>
<td>Hageman defect</td>
<td>Not required</td>
<td></td>
<td>Treatment not necessary</td>
</tr>
<tr>
<td>Von Willebrand</td>
<td>Von Willebrand disease</td>
<td>30%</td>
<td>Approximately 10 hours</td>
<td>Intermediate purity factor VIII concentrates that contain von Willebrand factor Some patients respond to DDAVP Cryoprecipitate¹</td>
</tr>
<tr>
<td>XIII</td>
<td>Factor XIII deficiency</td>
<td>5%</td>
<td></td>
<td>FFP Cryoprecipitate</td>
</tr>
</tbody>
</table>

¹ DDAVP: Desmopressin
Plasmin Inhibitors

- α2 Antiplasmin
  - Physiological.

- Aprotinin:  
  - Bovine parotid gland.

- Aminocaproic Acid

- Tranexamic Acid
Hemostatic Agents

- Absorbable Gelatin Foam
- Absorbable Gelatin Film
- Oxidized Cellulose
- Thrombin