Anti-Thrombotic Drugs

PHARMACOLOGY

DR HUNG DIEP

Overview

- Anti-thrombotic drugs include:
  - Anticoagulants
  - Fibrinolytics
  - Antiplatelets

Anticoagulants

- Interrupt the coagulation pathway to prevent clot formation
- Types include:
  - Indirect thrombin inhibitors
  - Vitamin K antagonists
  - Direct Factor Xa inhibitors
  - Direct thrombin inhibitors

Indirect Thrombin Inhibitors

- Anti-thrombotic effect is exerted by interaction with anti-thrombin
- Bind to anti-thrombin, which is a plasma protein that prevents the action of thrombin
  - Ultimately stops the conversion of fibrinogen to fibrin
- Includes:
  - Unfractionated heparin
  - Low molecular weight heparin
  - Fondaparinux

Unfractionated Heparin

- Binds to anti-thrombin III
  - Inhibits clotting factor proteases including Factors IIa, IXa, Xa
- No fibrinolytic activity
- Effect is monitored by Activated Thromboplastin Time
- Increases aldosterone production
- Reversal agent is protamine sulphate

Pharmacokinetics

- A: parenteral only (IV, SC)
- D: high protein binding
- M: liver and reticuloendothelial system metabolism
- E: metabolites excreted in urine

Indications

- Prevention/treatment of VTE
- Acute coronary syndrome
- Arterial thromboemboli
- Disseminated intravascular coagulopathy

Adverse Effects

- Bleeding
- Allergy
- Reversible alopecia
- Osteoporosis and fractures
- Heparin-induced thrombocytopenia
  - Occurs due to antibodies against heparin and platelet factor 4 compound
  - Usually an IgG compound so takes at least 5 days to form
  - Occurs in 1-4% of patients treated with unfractionated heparin for a minimum of 7 days
    - Rates lower with LMWH
  - Treated by cessation of heparin and use of direct thrombin inhibitors (e.g. bivalirudin)

Low-Molecular Weight Heparin

- Binds to anti-thrombin III to facilitate inactivation of Factor Xa
- Similar efficacy to unfractionated heparin
- No fibrinolysis
- No method of monitoring
- Poor efficacy of protamine in reversal

Pharmacokinetics

- A: subcutaneous only (90% bioavailability)
- D: high protein binding
- M: slight hepatic metabolism
- E: renal excretion

Indications

- Prevention/treatment VTE
- Acute coronary syndrome
- Arterial thromboemboli

Adverse Effects

- Bleeding
- Allergy
- Heparin-induced thrombocytopenia
  - Lower risk compared to unfractionated heparin

Vitamin K Antagonists

- Warfarin inhibits vitamin K epoxide reductase
- Decreases carboxylation of Factors II, VII, IX, X, and protein C and S
- There is an 8-12h delay in anticoagulant action due to depletion of protein C
- Effect can be monitored via the Prothrombin Time/INR

Pharmacokinetics

- Warfarin
  - A: oral (100% bioavailability)
  - D: 99% protein bound, small Vd
  - M: hepatic metabolism into inactive products by CYP450 enzymes
  - E: metabolites excreted in bile and urine

Indications

- Prevention/treatment of VTE
- Prevention of thromboembolism with prosthetic heart valves
- Prevention of stroke in those with increased embolic risk

Adverse Effects

- Bleeding
- Hepatic dysfunction
- Multiple interactions with other drugs
  - Particularly P450 CYP2C9 inducers or inhibitors

Direct Factor Xa Inhibitors

- Inhibits downstream activation of prothrombin
- Increases Prothrombin Time/INR
- Lower bleeding rates compared to Warfarin
- No need for monitoring of therapeutic action provided renal function is stable

Pharmacokinetics

- Rivaroxaban
  - A: oral, high bioavailability
  - D: high protein binding, moderate Vd
  - M: 2/3 hepatic metabolism
  - E: 1/3 excreted unchanged in the urine; metabolites excreted renally and faecally

Indications

- Prevention of stroke in AF
- Prevention/treatment of VTE
- Treatment of pulmonary embolism

Adverse Effects

- Bleeding
- Peripheral oedema
- Muscle spasm
- Hepatotoxicity

Direct Thrombin Inhibitors

- Exert their anticoagulant effect by directly binding to the active site of thrombin
  - Prevents subsequent activation of fibrinogen to fibrin
- Includes Dabigatran, Bivalirudin
  - Dabigatran is absorbed as a prodrug (dabigatran etexilate), which is then converted into the active form

Pharmacokinetics

- Dabigatran
  - A: oral, with rapid absorption and metabolism of the prodrug into its active form
  - D: moderate Vd
  - M: hepatic metabolism into its active form, minimal metabolism of the active for itself
  - E: urinary excretion in its active form

Indications

- Prevention/treatment of VTE
- Non-valvular AF

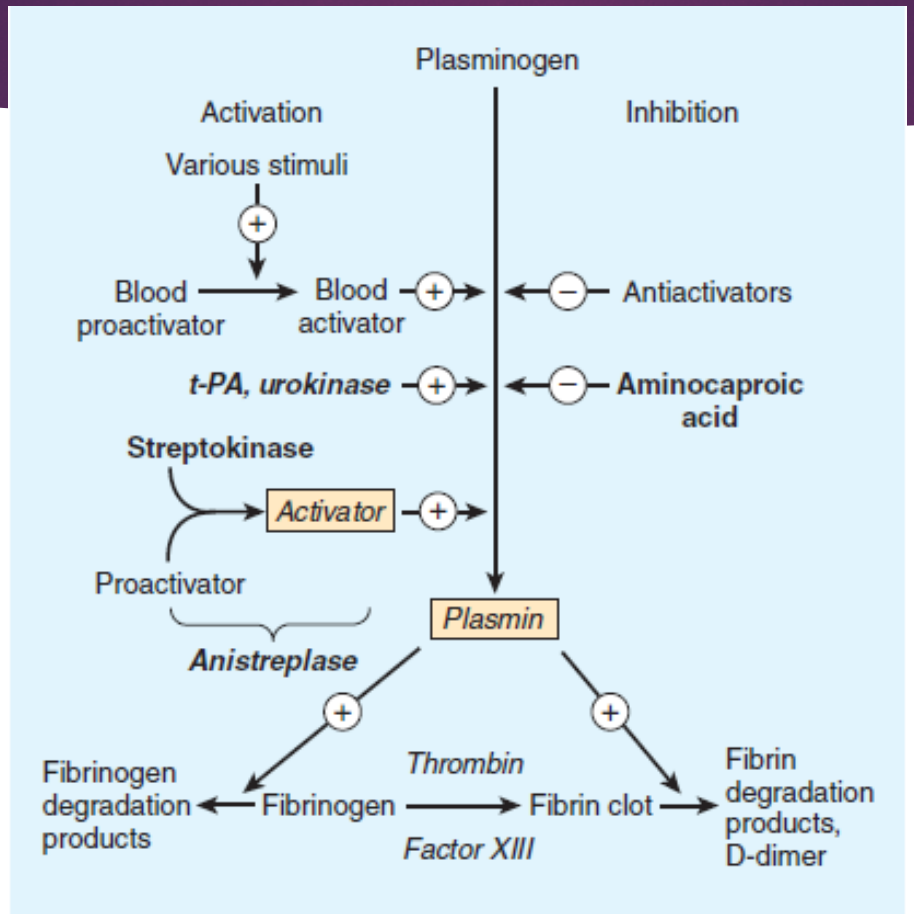
Adverse Effects

- Bleeding
  - Particularly gastrointestinal bleeding
- Gastritis

Fibrinolytics

- Preferentially activates plasminogen
  - Plasminogen is bound to fibrin
- Active plasmin results in breakdown of fibrin clots
- Plasmin naturally aims to confine fibrinolysis to the formed thrombus and avoid systemic activation
- Includes: alteplase, tenectaplase

Fibrinolytics



Pharmacokinetics

- Tissue Plasminogen Activator (t-PA)
  - A: IV
  - D: low Vd
  - M: hepatic metabolism
  - E: hepatically cleared

Indications

- Acute STEMI
- Massive pulmonary embolism
- Acute ischaemic stroke
- Acute VTE with haemodynamic instability

Adverse Effects

- Bleeding
- Allergy

Antiplatelets

- Platelet function is regulated by three categories of substances
  - Agents generated within the platelet that act within the platelet (thromboxane A2)
  - Agents generated within the platelet that interact with membrane receptors (ADP, prostaglandin)
  - Agents generated outside the platelet that interact with the platelet membrane

Thromboxane A2 Inhibitor

- Aspirin is rapidly converted into salicyclic acid
- Irreversible COX inhibitor
  - COX-1 is responsible for TxA2 production, which is a mediator of platelet aggregation and vasoconstriction
  - COX-2 is responsible for inflammation and cancer
- Results in decreased platelet aggregation
- Low dose aspirin preferentially blocks COX-1

Pharmacokinetics

- Aspirin
  - A: oral, high bioavailability
  - D: salicylate 80-90% protein bound
  - M: converted to salicylic acid in the gastrointestinal mucosa and liver
  - E: renal
    - Effects of aspirin last for the life of the platelet

Indications

- Acute coronary syndrome
- Atherosclerosis
- Inflammation
- Prevention of recurrent ischaemic stroke and TIA
- Prevention of pre-eclampsia

Adverse Effects

- Gastrointestinal irritation
- Bleeding
- Bronchospasm
- Angioedema

Phosphodiesterase Inhibitor

- Dipyridamole is a phosphodiesterase inhibitor
- Increases platelet cAMP and cGMP activity
- Results in inhibition of platelet function (adhesion and aggregation)
- Only effective in combination with Aspirin

Pharmacokinetics

- Dipyridamole
  - A: oral (70% bioavailability)
  - D: large Vd, 97-99% protein bound
  - M: liver
  - E: bile

Indications

- Prevention of recurrent ischaemic stroke and TIA

Thienopyridines

- Clopidogrel is a produg that is rapidly metabolised into its active form
- Irreversibly binds to platelet $P2Y_{12}$ (ADP) receptor
- Inhibits platelet aggregation for the life of the platelet
- Inhibits amplification of platelet activation

Pharmacokinetics

- Clopidogrel
  - A: oral, rapid
  - D: 94-98% protein bound
  - M: hepatic into active form
  - E: urine and faeces
    - Effect lasts for the life of the platelet

Indications

- Acute coronary syndrome
- Atherosclerosis

Adverse Effects

- Bleeding
- Skin reactions
- Gastrointestinal ulcer
- Pancytopenia