Oct 20 - Pharmacology of Anticoagulant Therapy

Introduction

Anticoagulants are generally ordered in the setting of venous thromboembolism (VTE), atrial fibrillation (for stroke prevention), mechanical heart valve, or arterial thrombosis (which can cause an infarct in major organs, such as the heart or the liver, etc.). The goal of therapy is to prevent (further) PE, stroke, or myocardial infarction or as prophylaxis to prevent VTE in medical or surgical patients.

Anticoagulants affect the coagulation cascade:

- The intrinsic pathway (measured by aPTT) contains factors XII, XI, V, VIII, IX, X, II, I
- The extrinsic pathway (measured by INR) contains factors VII, V, X, II, I
- Factors in the common pathway are highlighted in red – factor X, thrombin (II), and fibrin (I)

The generalizable risk of all anticoagulants is the risk of major or minor bleeds. Specific anticoagulants have specific risks as well. They are listed below.

The general contraindications for anticoagulants are:

- Active bleeding
- Recent CNS surgery
- Thrombocytopenia
- Renal impairment (if excreted renally)
- Hepatic impairment (if excreted/metabolized by the liver)

The general indications are:

- Treatment of VTE: provoked and unprovoked events
- Prophylaxis of VTE: surgical and medical patients
- In atrial fibrillation for stroke prevention
- Mechanical heart valves
- Arterial thrombosis

General use anticoagulants

Anticoagulant	Indications	Mechanism of Action	Notes
Unfractionated heparin (UH)	VTE treatment & prophylaxis Heparin flush for central lines, pumps, etc. Post-MI, angina *	Inactivating thrombin and Xa through an antithrombin(AT)-directed mechanism Heparin binds to AT through a high-affinity pentasaccharide present in 1/3 of UH molecules	**Variable pharmacokinetics**, needs monitoring of aPTT with therapeutic range of 60-80 seconds Administered parenterally (IV or subq) – instant max effect IV, gradual in subQ Hepatic clearance **Protamine sulfate** as antidote
Low molecular weight heparin	VTE treatment & prophylaxis Post-MI, angina Atrial fibrillation	Derived from heparin to yield fragments 1/3 the size of heparin w/ reduced binding to plasma proteins + cells Same mechanism of action, but reduced ability to inactivate thrombin (cannot bind to both AT and thrombin), but high Xa inhibition	More **predictable dose-response pharmacokinetics** and longer half-life compared to UH – no need to monitor and does not affect aPTT (measure Xa levels directly) Always subq, not IV Lower-risk of HIT, bleeds, and osteopenia than UH. Safe for use in pregnancy. *Renal clearance **Protamine sulfate** as partial-antidote
Warfarin	VTE treatment & prophylaxis Atrial fibrillation Mechanical heart valves Arterial thrombosis	Vitamin K antagonist – blocks synthesis of vitamin K dependent factors (II, VII, IX, X, proteins C and S) Action is dependent on the half-life of each factor, with effect mostly from reduced level of thrombin	Overlapping treatment with heparin needs, as anticoagulant effect occurs after 5-7 days Needs monitoring (INR 2.0 – 3.0), no standard fixed dose Bound to albumin in blood (contraindicated in liver disease) **Prothrombin Complex Concentrate (PCC)** to reverse quickly in case of serious bleed, **vitamin K** for general reversal Non-compliance or lack of monitoring is a contraindication
Direct Oral Anticoagulants	VTE treatment & prophylaxis Atrial fibrillation DVT/PE		Predictable pharmacokinetics, fixed dose, no monitoring Wide therapeutic windows **PCC** for reversal
Rivaroxiban		Directly inhibits factor Xa	Renal (66%) & hepatic (33%) clearance
Apaxiban		Directly inhibits factor Xa	Mostly hepatic clearance (75%)
Dabigotran		Direct thrombin inhibitor	Mostly *renal clearance(85%), hemodialysis for rapid reversal

*UH is also used for Extra Corporeal Membrane Oxigenation

Heparin-induced thrombocytopenia: antibodies form against heparin platelet factor 4 (PF4) complex and activate platelets, resulting in consumption and thrombosis. **Treatment of HIT**: stop heparin (or LMWH) and use alternative anticoagulant (danaparoid, argatroban, fondaparinux).

Anticoagulants in special situations

Anticoagulant	Indications	Mechanism of Action	Notes
Fondaparinux	VTE treatment & prophylaxis Treatment of HIT (off label)	Synthetic pentasaccharide chemically identical to that in heparin Specific anti-Xa activity higher than LMWH, does not inhibit thrombin	Always subq *Renal clearance Can reverse with recombinant FVIIa Long half-life (problem when overt bleeding)
Hirudins	HIT Acute coronary syndrome – PCI	Binds directly and irreversibly to thrombin to target the active site and the substrate binding site of fibrinogen (bivalent) Can inactivate fibrin-bound thrombin	Administered IV Short half-life, *renal clearance Monitoring to a target of 1.5 to 2.5 baseline PTT Expensive, need hospital admission Can be immunogenic
Argatroban	HIT	Univalent direct thrombin inhibitor of active site	Short half-life Requires monitoring Hepatic clearance (80%)
Danaparoid (heparinoid)	HIT	Binds to AT and inhibits preferably FXa compared to FIIa	Given IV or subq *Renal clearance Does not affect PTT b/c little anti-IIa activity Some (10%) in vitro antigenic cross-reactivity for heparin