Medicines and Transfusions

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* Platelet function
* Drugs affecting Coagulation;
  * Anti-platelet drugs
  * Anticoagulants
    * Oral anticoagulants
    * Parenteral anticoagulants
* Drugs affecting Haemoglobin levels
Platelet Function

**Figure 1: Normal Platelet Function and Antiplatelet Agents**

1. **Glyceryl trinitrate inhibits phosphodiesterase activity, thereby increasing cAMP and cGMP levels.** Elevated levels of cAMP and cGMP inhibit platelet activation.

2. **Aspirin inhibits cyclooxygenase and TXA2.**

3. **Release of cytoplasmic granules provokes expression of GP Ib/IIa receptor.**

4. **GPIb/IIa receptor now has increased affinity for fibrinogen which cross-links platelets.** The result is a platelet aggregate.

5. **GP Ib/IIa antagonists prevent fibrinogen binding to activated platelets.**

6. **Binding of TXA2 to ADP receptors on platelets activates platelet shape change.**

7. **TXA2 inhibits adenylate cyclase.**

8. **Platelet aggregation.**
Involved in haemostasis and formation of blood clots

Present along the surface of the blood vessel wall, which is lined by endothelial cells. The endothelium prevents anything from sticking to it.

When there is an injury or cut, and the endothelial layer is broken, the tough fibres that surround a blood vessel are exposed to the liquid flowing blood.

Platelets that react first to injury
The tough fibres surrounding the vessel wall attract platelets like a magnet, and the platelets then clump onto these fibres, providing the initial seal to prevent bleeding and the leak of red blood cells and plasma through the vessel injury.

- Lifespan of 5-9 days
- Thrombocytopenia (low platelets) → bleeding
- Thrombocytosis (↑ platelets) → clotting
Anti-platelet Drugs

- **Aspirin** - induces irreversible inactivation of **COX-1**, which lasts the lifetime of platelet
- **Dipyridamole** - inhibits the uptake of adenosine into erythrocytes, platelets, and endothelial cells
- **Clopidogrel** - prodrug, of which its metabolite is an inhibitor of platelet aggregation
- **Prasugrel** - irreversible inhibitor of platelet activation and aggregation
- **Ticagrelor** - selective adenosine diphosphate (ADP) receptor antagonist acting on the P2Y\textsubscript{12} ADP-receptor that can prevent ADP-mediated platelet activation and aggregation
Anti-platelet Drugs

* Reported side effects on blood:
  * Thrombocytopenia (low platelet count)
  * Aplastic anaemia—when body stops making new red blood cells
  * Thrombotic thrombocytopenic purpura (TTP)—the development of tiny blood clots
  * Neutropenia—low white blood cell count
  * Agranulocytosis
<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Dipyridamole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of Action</strong></td>
<td>COX-1 inhibitor</td>
<td>P2Y12 inhibitor</td>
<td>P2Y12 inhibitor</td>
<td>P2Y12 inhibitor</td>
<td>Phosphodiesterase inhibitor</td>
</tr>
<tr>
<td><strong>Onset of action after loading dose</strong></td>
<td>Minutes</td>
<td>1 hour</td>
<td>2 hours</td>
<td>2 hours</td>
<td>Slow</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>0.5 hour</td>
<td>6 hours</td>
<td>7 hours</td>
<td>7-9 hours</td>
<td>15 hours</td>
</tr>
<tr>
<td><strong>Bleeding risk</strong></td>
<td>+</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Time to normal platelet function after stopping</strong></td>
<td>5-7 days</td>
<td>5-7 days</td>
<td>5-7 days</td>
<td>3-5 days</td>
<td>24 hours</td>
</tr>
<tr>
<td><strong>Elective surgery</strong></td>
<td>Stop 7 days before</td>
<td>Stop 7 days before</td>
<td>Stop 7 days before</td>
<td>Stop 7 days before</td>
<td>Stop 24 hours before surgery</td>
</tr>
<tr>
<td><strong>Reported side effects on blood results</strong></td>
<td>N/A</td>
<td>Leucopenia, Thrombocytopenia, Agranulocytosis</td>
<td>Anaemia, Thrombocytopenia</td>
<td>N/A</td>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>
**Bleeding Risks**

- **On Aspirin**
  - Surgical bleeding ↑ 2.5-20%
  - No increase in surgical mortality or morbidity
  - Post-op intracerebral haematoma ↑ in neurosurgery

- **On dual therapy**
  - Surgical bleeding ↑ 30%
  - No increase in surgical mortality or morbidity
  - Except intracranial surgery
* Oral Anticoagulants;
  1. Coumarins: Warfarin, acenocoumarol, phenindione
  2. Dabigatran
  3. Rivaroxaban
  4. Apixaban

* Parenteral Anticoagulants;
  a. Heparins – unfractionated and low molecular weight
  b. Fondaparinux
  c. Argatroban
Mechanism of action of Anticoagulants

- **Warfarin**
  - Intrinsic activation: Surface contact
    - Factor XII
    - Factor XI
    - Factor VIII
    - Factor IXa
    - Factor X
  - Extrinsic activation: Vessel injury
    - Factor VII

- **Apixaban**
  - Prothrombin
  - Factor Xa
  - Thrombin
  - Fibrinogen → Fibrin

- **Rivaroxaban**
  - Dabigatran etexilate

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1. **Coumarins eg. warfarin**
   - Antagonise effect of vitamin K
   - Block clotting factors II, VII, IX & X
   - Half-life of approx. 40 hours
   - Increases patients’ INR reading
   - Increases Prothrombin Time
   - Shouldn’t affect APTT (but reports of prolonged APTT)
   - Shouldn’t affect platelets
2. Dabigatran - direct thrombin inhibitor

- Increases APTT
- Don’t use INR tests to measure dabigatran levels – unreliable
- Half-life approx. 11 hours
- Side effects; anaemia (common), thrombocytopenia (uncommon), low Hb (uncommon)
3. Rivaroxaban - direct factor Xa inhibitor

- Prolongs Prothrombin Time especially when patient is bleeding
- Increases APTT
- Does not affect platelets
- Half-life = 5-9 hours (longer in elderly)
- Side Effects; Anaemia (common), Thrombocythemia (uncommon)
4. Apixaban - direct factor Xa inhibitor
- Prolongs Prothrombin Time especially when patient is bleeding
- Increases APTT
- Does not affect platelets
- Half-life = 12 hours
- Side Effects: Anaemia (common), Thrombocythemia (uncommon)
Parenteral Anticoagulants

a. Heparins;
  i) Unfractionated heparin – dose adjusted according to APTT levels
     * Very short half-life
     * Side effects; Thrombocytopenia (HIT)
  ii) Low molecular weight heparin – dose depending on weight of patient
     * Longer half-life than UFH
     * Side effects; Thrombocytopenia (HIT)
b. Fondparinux;
- Synthetic & selective inhibitor of activated Factor Xa
- Interrupts blood coagulation cascade and inhibits thrombin formation and thrombus development
- Does not inactivate thrombin (activated Factor II)
- Has no effects on platelets
- Used in patients with history of HIT or patients who refuse LMWH on religious grounds
- Half-life; 17 hours in young and 21 hours in elderly
- Side Effects; Bleeding (common), anaemia (common)
c. Argatroban;
- Direct thrombin inhibitor
- Used for treatment of patients with heparin-induced thrombocytopenia (HIT)
- Dose adjusted according to APTT ratio
- Very short half-life
- Side Effects; Anaemia (common), coagulopathy (uncommon), leukopenia (uncommon)
Drugs affecting Haemoglobin Levels

- Aspirin & NSAIDs
- Dapsone
- Cephlasporins (eg. Cefalexin)
- Sulfasalazine
- Levofloxacin
- Nitrofurantoin
- Proton Pump Inhibitors (eg. Lansoprazole)
- Anabolic steroids
Platelet function

Drugs affecting Coagulation;
  * Anti-platelet drugs
  * Anticoagulants
    * Oral anticoagulants
    * Parenteral anticoagulants

Drugs affecting Haemoglobin levels