Drugs and Blood

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Overview

• Medication and bleeding risk reduction
  – Discontinuation of drugs that increase bleeding risk
    – Understand how they work
    – When to stop for elective procedures
    – Management for emergency surgery
  – Reducing blood loss peri-operatively
    – Understand how medication can help
    – Aware of associated risks
• Medication known to increase risk of bleeding:
  – Anticoagulants
  – Antiplatelets
  – NSAIDs
  – Herbal Medicines
Anticoagulants

• An anticoagulant is a drug which is known to inhibit the clotting cascade and hence prevent clot formation

• Includes:
  – Warfarin (antagonise the effects of vitamin K)
  – NOACs
  – Low Molecular Weight Heparin
Indications for anticoagulation

- Stroke prophylaxis in Atrial Fibrillation
- Stroke prophylaxis in patients with either mechanical or tissue heart valves
- Treatment of DVT or PE
- Thromboprophylaxis following hip or knee replacement surgery

Decision to stop treatment is always a balance between risk and benefit
Things to consider:

- Consequence of withholding anticoagulant
- Associated risk of bleeding with individual surgery or procedure
- Alternative anticoagulation available for that individual patient
ANTICOAGULANT EFFECT OF NOACs

The coagulation cascade is a series of reactions involving coagulation factors that ultimately results in the formation of a blood clot. The NOACs directly inhibit one specific coagulation factor in the cascade, whereas warfarin prevents the coagulation process by suppressing the synthesis of several vitamin K-dependent coagulation factors.

INTRINSIC (CONTACT ACTIVATION) PATHWAY
Activated by contact of the vessel wall with lipoprotein particles or bacteria
- Factors IX
  - Factors XI, XII
  - Factor X
  - Factor Xa
  - Prothrombin (Factor II)

EXTRINSIC (TISSUE FACTOR) PATHWAY
Activated in response to tissue injury
- Factor VII
  - Tissue factor
  - Factor X
  - Factor Xa
  - Thrombin (Factor IIa)
  - Fibrinogen (Factor I)
  - Fibrin (Factor Ia)

WARFARIN
- Usual dose: 1–10mg od.
- Bioavailability: 99%
- Peak plasma level: 72–96 hrs.
- Half-life: 20–60 hrs.
- Renal excretion: <1%. Liver metabolism: yes.
- Drug-drug and drug-food interactions: numerous.

Sources:

Editorial advice: Sarah Whiddon, consultant anticoagulation pharmacist, South West Hampshire Hospitals Trust

Infographics: MSV
Warfarin

- Antagonises the effects of vitamin K
- Still commonly prescribed despite the newer anticoagulants now available
- Has a long half life and the dose prescribed is dependent on the individual patient
- Minor to moderate surgery not always needed to be withheld
• Elective major surgery usually requires omitting warfarin for approximately 5 days and bridging with an alternative anticoagulant

• Can be reversed using phytomenadione for emergency surgery
Dabigatran

- Reversible direct thrombin inhibitor
- Prior to elective surgery, should be stopped at a time dependent on the associated risk of surgery and the patient's renal function
- Restarted as soon as possible after the procedure or intervention
- Can be reversed using praxbind
<table>
<thead>
<tr>
<th>Renal function (CrCL in mL/min)</th>
<th>Estimated half-life (hours)</th>
<th>Stop dabigatran before elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High risk of bleeding or major surgery</td>
</tr>
<tr>
<td>≥ 80</td>
<td>~ 13</td>
<td>2 days before</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 hours before</td>
</tr>
<tr>
<td>≥ 50-&lt; 80</td>
<td>~ 15</td>
<td>2-3 days before</td>
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<tr>
<td></td>
<td></td>
<td>1-2 days before</td>
</tr>
<tr>
<td>≥ 30-&lt; 50</td>
<td>~ 18</td>
<td>4 days before</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-3 days before (&gt; 48 hours)</td>
</tr>
</tbody>
</table>
Praxbind (idarucizumab)

• Specific reversal agent for dabigatran

• Recommended dose is 5g (a second dose may be considered in depending on the patients clotting times)

• Maximum daily dose has not been investigated

• Dabigatran can be re-initiated 24 hours after administration of praxbind

• Expensive!
Factor Xa inhibitor’s

- Rivaroxaban, Apixaban and edoxaban
- Prevents thrombin formation and development through inhibiting factor Xa
- Should be stopped at least:
  - 48 hours prior to elective surgery with high or moderate risk of bleeding
  - 24 hours prior to elective surgery with a low risk of bleeding
- Restarted as soon as possible after the procedure or intervention
• There is currently no antidote for factor Xa inhibitors

• Andexanet is currently under development which should be available within the next year

• Recombinant factor VIIa or prothrombin complex concentrate (PCC) have been shown to reverse the effects although there is limited evidence which supports this
Low Molecular Weight Heparin

- Often used to bridge the gap between stopping oral anticoagulants and surgery
- Risk of Heparin Induced Thrombocytopaenia
- Stopped at least 12-24 hours before surgery, epidural or spinal anaesthesia
Antiplatelets

• Decrease platelet aggregation and inhibit thrombus formation

• Usual Indications
  – Prevention of atherothrombotic events in patients with a history of ischaemic disease or in Acute Coronary Syndrome
  – Prevention of atherothrombotic or thromboembolic events in AF (if warfarin is unsuitable)
  – Treatment of TIA or acute stroke
• There are various different antiplatelets available
  – ADP receptor antagonists – clopidogrel, prasugrel & ticagrelor
  – COX inhibitors – Aspirin
  – PDE inhibitors – Dipyridamole
  – GP IIb/IIIa inhibitors – Tirofiban, abciximab
**NSAIDs**

- Associated with an increased risk of bleeding due to antiplatelet effect
- Most clinicians recommend stopping before elective surgery
- COX2 specific inhibitors are not associated with an increased bleeding risk and can be continued
Herbal Medicines

• Often not disclosed by patients

• Common to consider:
  – High dose garlic
  – Ginkgo Biloba
  – Ginger
  – High dose vitamin E
  – Ginseng

Always remember to ask about herbal medicines!
Medication used to reduce blood loss peri-operatively

- Antifibrinolytic agents
  - Tranexamic acid
- Desmopressin
Tranexamic Acid

• **Indications:**
  – Prevention and treatment of haemorrhage due to local or general fibrinolysis
  
• Inhibits fibrinolysis and reduces clot breakdown

• Inhibits plasminogen activation and therefore prevents conversion to plasmin

• Dose is reduced in renal impairment
Tranexamic Acid

- Proven to reduce the probability of receiving a blood transfusion by over 30% depending on the type of surgery
- Risk of thromboembolic events occurring
- ADRs include convulsions, hypersensitivity reactions, visual disturbances, nausea and diarrhoea
Desmopressin

• Synthetic analogue of vasopressin
• Increases the plasma levels of factor VIII and vWF
• Enhances platelet adhesion to the wall
• Used for mild to moderate haemophilia or von Willebrands disease patients undergoing surgery or following trauma
• Lack of clinical evidence suggesting its use in patients who do not have congenital bleeding disorders
- Dose can be repeated at 12 hourly intervals, however, response can diminish after successive doses
- Caution to prevent fluid overload in patients
- Vasodilation may occur resulting in tachycardia, hypotension and facial flushing
Summary

• Some medication can increase the risk of bleeding and this can be minimised in elective cases.

• Tranexamic acid can be used to help reduce blood loss.

• Alternatives such as desmopressin can also be used in patients with congenital bleeding disorders.