Warfarin

Warfarin is an oral anticoagulant which inhibits the reduction of vitamin K to its active hydroquinone form, which in turn acts as a cofactor in the formation of clotting factor II, VII, IX and X (mnemonic = 1972) and protein C .

Indications

- venous thromboembolism: target INR = 2.5, if recurrent 3.5
- atrial fibrillation, target INR = 2.5
- mechanical heart valves, target INR depends on the valve type and location. Mitral valves generally require a higher INR than aortic valves.

Patients on warfarin are monitored using the INR (international normalised ration), the ratio of the prothrombin time for the patient over the normal prothrombin time. Warfarin has a long half-life and achieving a stable INR may take several days. There a variety of loading regimes and computer software is now often used to alter the dose.

Factors that may potentiate warfarin

- liver disease
- P450 enzyme inhibitors, e.g.: amiodarone, ciprofloxacin
- cranberry juice
- drugs which displace warfarin from plasma albumin, e.g. NSAIDs
- inhibit platelet function: NSAIDs

Side-effects

- haemorrhage
- teratogenic, although can be used in breast-feeding mothers
- skin necrosis: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis
- purple toes

Venous thromboembolism: risk factors

Common predisposing factors include malignancy, pregnancy and the period following an operation. The comprehensive list below is partly based on the 2010 SIGN venous thromboembolism (VTE) guidelines:

General

- increased risk with advancing age
- obesity
- family history of VTE

- pregnancy (especially puerperium)
- immobility
- hospitalisation
- anaesthesia
- central venous catheter: femoral >> subclavian

Underlying conditions

- malignancy
- thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
- heart failure
- antiphospholipid syndrome
- Behcet's
- polycythaemia
- nephrotic syndrome
- sickle cell disease
- paroxysmal nocturnal haemoglobinuria
- hyperviscosity syndrome
- homocystinuria

Medication

- combined oral contraceptive pill: 3rd generation more than 2nd generation
- hormone replacement therapy
- raloxifene and tamoxifen
- antipsychotics (especially olanzapine) have recently been shown to be a risk factor

SIGN also state that the following are risk factors for recurrent VTE:

- previous unprovoked VTE
- male sex
- obesity
- thrombophilias

Antiphospholipid syndrome: (paradoxically) prolonged APTT + low platelets

The combination of a prolonged APTT and thrombocytopenia make antiphospholipid syndrome the most likely diagnosis

Antiphospholipid syndrome

Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia. It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)

A key point for the exam is to appreciate that antiphospholipid syndrome causes a paradoxical rise in the APTT. This is due to an ex-vivo reaction of the lupus anticoagulant autoantibodies with phospholipids involved in the coagulation cascade

Features

- venous/arterial thrombosis
- recurrent fetal loss
- livedo reticularis
- thrombocytopenia
- prolonged APTT
- other features: pre-eclampsia, pulmonary hypertension

Associations other than SLE

- other autoimmune disorders
- lymphoproliferative disorders
- phenothiazines (rare)

Management - based on BCSH guidelines

- initial venous thromboembolic events: evidence currently supports use of warfarin with a target INR of 2-3 for 6 months
- recurrent venous thromboembolic events: lifelong warfarin; if occurred whilst taking warfarin then increase target INR to 3-4
- arterial thrombosis should be treated with lifelong warfarin with target INR 2-3

ITP

Idiopathic thrombocytopenic purpura (ITP) is an immune mediated reduction in the platelet count. Antibodies are directed against the glycoprotein IIb-IIIa or Ib complex.

ITP can be divided into acute and chronic forms:

Acute ITP

- more commonly seen in children
- equal sex incidence
- may follow an infection or vaccination
- usually runs a self-limiting course over 1-2 weeks

Chronic ITP

- more common in young/middle-aged women
- tends to run a relapsing-remitting course

Evan's syndrome

- ITP in association with autoimmune haemolytic anaemia (AIHA)

Warfarin overdose

The following is based on the BNF guidelines, which in turn take into account the British Committee for Standards in Haematology (BCSH) guidelines. A 2005 update of the BCSH guidelines emphasised the preference of prothrombin complex concentrate over FFP in major bleeding.

Major bleeding	Stop warfarin Give intravenous vitamin K 5mg Prothrombin complex concentrate - if not available then FFP*
INR > 8.0 **Minor bleeding**	Stop warfarin Give intravenous vitamin K 1-3mg Repeat dose of vitamin K if INR still too high after 24 hours Restart warfarin when INR < 5.0
INR > 8.0 **No bleeding**	Stop warfarin Give oral vitamin K 1-5mg Repeat dose of vitamin K if INR still too high after 24 hours Restart when INR < 5.0
INR 5.0-8.0 **Minor bleeding**	Stop warfarin Give intravenous vitamin K 1-3mg Restart when INR < 5.0
INR 5.0-8.0 **No bleeding**	Withhold 1 or 2 doses of warfarin Reduce subsequent maintenance dose

*as FFP can take time to defrost prothrombin complex concentrate should be considered in cases of intracranial haemorrhage