Pharm-12B01 How does warfarin exert its anti-coagulant effect? What methods can be used to reverse the effects of warfarin prior to surgery?

**Background**

Warfarin is an oral anticoagulant commonly used for treatment and prophylaxis of patients with:
- atrial fibrillation
- venous thromboembolic disease
- prosthetic heart valves

**Mechanism of Action**

Warfarin exists as two enantiomers → S-warfarin is 3x more potent than R-warfarin
Warfarin competitively inhibits vitamin K-epoxide reductase (VKORC1)

VKORC1 converts vitamin K from oxidised to reduced form

Vitamin K in reduced form → γ-carboxylate glutamate residues of clotting factors II, VII, IX and X as well as protein C and S → activation

warfarin → ↓active form of factors II, VII, IX, X → anticoagulant effect
warfarin → ↓active form of protein C and S → initial hypercoagulable state

warfarin only disrupts the production of new clotting factors, it has no effects on circulating clotting factors

peak clinical effect occurs when significant fall in concentrations of factor II and X, which usually takes 5 ~ 7 days

**Reversal**

The following reversal strategies may be either used alone or in combination

*(1) Stopping warfarin*

S-warfarin is eliminated via oxidation predominantly by CYP2C9 (and to a lesser extent by CYP3A4 and 1A2) → inactive metabolites

Elimination half-life of S-warfarin is 29 hours
∴ in patients with normal hepatic metabolic and synthetic functions → take 4 ~ 5 days for INR to normalise

*(2) Vitamin K*

Can be given either enterally or parenterally (IV, IM) (bioavailability ≈ 100%)

Low dose vitamin K (1 ~ 2.5 mg) will slowly reduce INR over 24 hours but often will not result in complete reversal and would not significant affect re-establishment of anticoagulation with warfarin

High dose vitamin K (10 mg) will slowly reduce INR over 12 hours .∴ often given together with clotting factors (e.g. FFP)*
(3) **Fresh frozen plasma**
Plasma from donated blood, which contains all clotting factors
∴ immediately reverses coagulopathy
However, short duration of action (24 ~ 48 hours) ∴ reserved for active bleeding
Dose 2 ~ 4 units depending on INR and bleeding risk

Disadvantages = relatively large fluid volume, possible transfusion reactions (e.g. immune reaction, TRALI, infection, etc)

(4) **Prothrombinex**
Human plasma derivative containing concentrates of factors II, IX and X
∴ immediately reverses coagulopathy
Dose 25 ~ 50 IU/kg

Advantages = reliable reversal, smaller fluid volume, avoids transfusion complications associated with FFP
Disadvantages = expensive

(5) **Recombinant activated factor VII**
Controversial treatment, present in some guidelines
Indication = life threatening bleed with significantly elevated INR
Given together with vitamin K and FFP
Disadvantage = thromboembolic complications

**Examiner’s comments**

**Mechanism**
Generally the mechanism of action section of the question was well answered.
Most appreciated the fact that warfarin blocked the conversion of vitamin K from its oxidised state to its reduced form therefore being unable to gamma-carboxylate glutamate residues of factors 2, 7, 9 and 10 as well as the anti-coagulant proteins C and S.
The majority of candidates appreciated the significance of the half lives of each and the subsequent propensity of a hypercoagulable state early in warfarin treatment.

**Reversal**
Management of warfarin reversal lends itself to a discussion of time course and urgency and most candidates recognised this.
However discussion focused mainly on vitamin K and fresh frozen plasma administration, albeit generally of a high quality.
Not all appreciated that stopping the drug prior to elective surgery was an appropriate course of action.
Only half mentioned prothrombin complex concentrates ('Prothrombinex') and a handful of answers mentioned activated factor 7 in the 'excessively' warfarinised bleeding patient. There were a few excellent answers with a complete listing of constituents and doses of the latter two agents.