Musgrove Park Hospital	**Guideline**
Title: Guidelines for the management of warfarin reversal [key words : Beriplex, Octaplex, PCC, vitamin K, anticoagulant, anticoagulation]	
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Applies to: Staff managing patients on warfarin	**Exclusions:**
Purpose; To promote optimal management of warfarin reversal	

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1. Key points

Treatment with warfarin is effective anti-thrombotic therapy. Its therapeutic use is monitored by the INR (international normalised ratio). The effective half life of warfarin ranges from 20 – 60 hours with a mean of 40 hours. The duration of effect is 2 – 5 days. Annual bleeding rates of fatal, major and minor bleeding for warfarinised patients have been reported as 0.8%, 4.9% and 15% respectively in observational studies (Landefeld & Beyth, 1993). The two variables most consistently associated with bleeding risk are intensity of anticoagulation and age. The risk of bleeding at an INR > 7.0 is 40 times the risk at an INR in the range of 2.0 – 2.9 and 20 times the risk at an INR in the range of 3.0 – 3.9 (Palareti et al, 1996). The risk of bleeding during warfarin therapy is also influenced by the intensity and variability of anticoagulation and duration of anticoagulation (increased bleeding risk when first started on anticoagulation therapy) and increased by the following patient risk factors:

1. Age > 65 years
2. Uncontrolled hypertension
3. Diabetes
4. Renal failure
5. Hepatic failure
6. Previous stroke
7. Trauma and recent surgery
8. Anti-platelet drugs
9. Previous major bleeding

Management depends on the perceived risk of bleeding and the presence/absence of minor/major haemorrhage.

2. The bleeding patient

Bleeding whilst on oral anticoagulants increases significantly with INR > 5.0. Therapeutic decisions depend on INR and the severity of bleeding.

2.1 Major/life threatening bleeding

Major/life threatening bleeding includes the following:

1. Intracranial bleeding
2. Intra-ocular (not conjunctival) bleeds
3. Retroperitoneal bleed
4. Compartment syndrome
5. Pericardial bleeds
6. Active bleeding and haemodynamic compromise

Major/life threatening bleeding requires rapid and complete reversal of anticoagulation. This cannot be achieved by simple warfarin withdrawal and needs administration of vitamin K together with coagulation factor replacement. Patients on anticoagulants may be bleeding for other reasons than the effect of the anticoagulant so blood should also be taken for FBC, INR, APTT and fibrinogen. All patients should be evaluated to identify if there is a local anatomical reason for bleeding.

1. Send urgent clotting screen (APTT, PT, INR and fibrinogen) in addition to any other clinically indicated bloods
2. Obtain relevant history and evaluate for local anatomical reason for bleeding. Bleeding may occur when patients are not over-anticoagulated but it may still be necessary to reverse anticoagulation and identify cause of bleeding
3. Warfarin should be stopped but dose omission alone has no significant role in the emergency situation due to slow resolution of anticoagulant effect.
4. Give prothrombin complex concentrate (PCC) over 10 – 15 minutes (Appendix A).
5. Give vitamin K (Konakion MM) 5mg by slow intravenous injection
6. Check clotting 30 minutes after PCC infusion completed to assess degree of correction of INR.

FFP is not the optimal form of coagulation factor replacement because the recommended volume (15ml/kg = 1000ml for 70kg patient) is insufficient to completely correct the coagulopathy. A dose of 15ml/kg provides the average adult with 640 IU of factor IX, sufficient to raise the factor IX level by only 9%. When the INR is > 4.0 the factor IX level is usually less than 20% and may be less than 10%.

2.2 Minor bleeding

If a patient presents with an INR > 8.0 the aim of intervention is to bring the INR back into the therapeutic range without rendering the patient resistant to further warfarin therapy.

1. Stop warfarin
2. Consider giving vitamin K (Konakion MM) 2.5 - 5mg orally or 1mg slow intravenous injection
3. Recheck clotting at 24 hours and daily thereafter
4. Restart warfarin when INR < 5.0

3. Patient not bleeding but INR too high

Withholding warfarin results in slow reversal of anticoagulation: after stopping warfarin for 24, 48 and 72 hours 33%, 68% and 89% patients respectively returned to therapeutic range (Cosgriff, 1956). Thus the majority of anticoagulated patients will return to therapeutic range within 3 days of stopping therapy. Importantly, a delay of 24 - 48 hours is seen before the maximal rate of fall of INR begins.

3.1 INR > 8.0 bleeding absent

1. Stop warfarin
2. Give vitamin K (Konakion MM) 2.5 – 5mg orally or 1mg intravenously
3. Measure INR daily
4. Resume warfarin therapy at reduced dose once INR < 5.0

3.2 INR 5.0 – 8.0 bleeding absent

Low risk of bleeding

1. Stop warfarin
2. Measure INR daily
3. Restart warfarin when INR < 4.0

High risk of bleeding

Defined as patients with additional risk factors (see key points above)

1. Stop warfarin
2. Consider vitamin K orally (Konakion MM 1 – 2mg) or slow intravenous infusion (Konakion MM 0.5 – 1mg)
3. Measure INR daily
4. Restart warfarin when INR < 5.0

3.3 INR <5.0 but >0.5 above target bleeding absent

1. Reduce dose or stop warfarin
2. Restart when INR < 4.0

4. Rapid reversal of warfarin prior to urgent surgical procedure

Urgent means clinically essential, not administratively convenient, to do immediate surgery.

4.1 For reversal in 4 – 24 hours

Vitamin K (Konakion MM) 1mg slow intravenous injection

4.2 For reversal within 1 hour

Prothrombin complex concentrate (PCC) (see appendix 1 for dosage) via slow iv bolus over 10 – 15 minutes.

5. Reintroducation of oral anticoagulants

1. The timing of reintroduction of oral anticoagulants will depend on the risk of post-operative haemorrhage. Generally warfarin can be restarted once haemostasis is achieved. Warfarin will take 48 – 72 hours to reach full effect – this may influence the decision to restart.

References

Guidelines on oral anticoagulation: third edition British Journal of Haematology 1998 101:374 – 87

Guidelines on oral anticoagulation (warfarin): third edition – 2005 update British Journal of Haematology 2005 132: 277 – 285

The management of coumarin-induced overanticoagulation. Makris, M et Watson HG British Journal of Haematology 2001 114: 271 – 280

Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Palareti G. et al. Lancet 1996 348: 423 – 428.

Appendix A

Administration of prothrombin complex concentrate (PCC)

At present there are two brands of PCC that may be stocked: Beriplex and Octaplex. Both are produced by fractionation of pooled plasma and contain factors II, VII, IX and X.

PCC is held in stock by the transfusion department and should be requested using a transfusion request form. Urgent requests can be made via bleep 2273. Dosage is related to factor IX content and is determined by INR of the patients. Dosage differs for the two PCC products – as shown below.

Beriplex dosage

Initial INR	2.0 – 3.9	4.0 – 6.0	> 6.0
Beriplex dose	25 u/kg	35 u/kg	50u/kg

Maximum single Beriplex dose should not exceed 5,000 iu

Octaplex dosage

Initial INR	2.0 – 2.5	2.6 – 3.0	3.1 – 3.5	>3.5
Octaplex dose	25iu/kg	35 iu/kg	45 iu/kg	50 iu/kg

Maximum single Octaplex dose should not exceed 3,000 iu.

PCCs are blood products and should be prescribed using a blood product prescription. The prescription should include product name and dose. The rationale for use of PCC should be documented in the notes.

Contra-indications

PCCs can give rise to thrombosis (arterial and venous) and DIC. DIC and uncompensated liver disease are contra-indications.

Octaplex is contraindicated if the patient has a known allergy to heparin or a history of heparin induced thrombocytopenia as it contains heparin.

Both Beriplex and Octaplex are packaged as a dry powder requiring reconstitution with supplied diluent in septic conditions prior to administration. Both may be administered by slow intravenous infusion over 10 – 15 minutes.

Appendix B

Vitamin K

Vitamin K will reverse the effect of warfarin partially or wholly depending on the route of administration and the dose used.

Intravenous administration results in rapid correction of anticoagulation with significant effects on INR in 4 – 6 hours. Oral vitamin K is much slower: satisfactory reversal is achieved in 24 hours.

In life-threatening bleeding intravenous vitamin K should be used. A dose of 5mg provides complete correction in most patients but does not render the patient resistant to re-anticoagulation.

In the absence of bleeding or minor bleeding the aim is to bring the INR back into the therapeutic range. Low dose (0.5 – 1.0mg) intravenous vitamin K or 1 – 2.5mg oral vitamin K may be used. Different vitamin K preparations have variable oral bioavailability. Konakion MM is almost completely absorbed, making it the vitamin K preparation of choice. Repeated doses may be given at 24 hour intervals if required.

Allergic reactions following intravenous administration are rare with new preparations of vitamin K.

Subcutaneous absorption of vitamin K is erratic and not recommended.