

ORAL ANTICOAGULANTS (WARFARIN)

- The risk of bleeding is highest in the first month of therapy.¹
- Under coagulation is wasteful and over anticoagulation is dangerous; both occur commonly. Benefit is seen only with an INR of greater than 2.0.
- Patients commencing warfarin should be counselled about warfarin's actions, interactions and side effects.
- Changes in the patient's medical condition or drug therapy may alter anticoagulant control and require more frequent monitoring.

Warfarin a coumarin anticoagulant is used for the prevention and treatment of thromboembolism. Effective control requires knowledge of all aspects of the patient's health, including concurrent illness and drug therapy. The list of indications for oral anticoagulation has grown considerably and more recently includes uncomplicated atrial fibrillation.

PHARMACOLOGY

Warfarin acts by depressing the synthesis of vitamin K dependent coagulation factors II, VII, IX, X, the anticoagulant protein C and its cofactor protein S. It is extensively bound to plasma proteins with a half life of approximately 36 hours. Warfarin acts indirectly and has no effect on existing clots. A therapeutic effect is usually apparent by 24 hours but the peak effect may not be achieved for 2-3 days and may last 5 days. There is a direct relationship between the dose of warfarin and the anticoagulant response in normal subjects but marked variation in the response between subjects.²

USE OF ORAL ANTICOAGULANTS²

The following are conditions for which oral anticoagulants are used but differences of opinion remain as to the indications for their use in some of these.

- Prophylaxis and treatment of deep vein thrombosis
- Arterial grafts
- Atrial fibrillation
- Cardiomyopathy
- Prosthetic heart valves (xenograft and mechanical)
- Lupus-like anticoagulant with clinical thrombosis
- Embolic complications of rheumatic heart disease
- Pulmonary embolism
- Carotid disease
- Acute myocardial infarction
- Peripheral arterial disease
- Congenital Factor deficiencies

CONTRA-INDICATIONS³

Contra-indications to warfarin therapy include;

- Pregnancy
Warfarin is a teratogen and can cause fetal haemorrhage. It should be avoided particularly in the first and third trimester (risk of haemorrhage).
- Non-thromboembolic stroke
- Severe renal and hepatic disease
- Haemorrhagic conditions
- Hypersensitivity to warfarin.

COUNSELLING FOR PATIENTS COMMENCING WARFARIN.

- Take warfarin at the same time each day to facilitate interpretation of INR results.
- A missed dose must be recorded. It should be taken within 12 hours and the normal dosing schedule resumed the next day.
- Patients should be given information about warfarin's actions, interactions and side-effects.

Discuss:

- over the counter (OTC) drugs especially aspirin and NSAIDs
- significant changes in intake of food high in Vitamin K (e.g. liver, green leafy vegetables) affects the action of warfarin and more frequent monitoring may be required.
- alcohol consumption: this should not exceed 2 units/day, which has no effect on the INR

- signs of over anticoagulation: e.g. excessive bruising, epistaxis, bleeding gums, severe headache, haematuria, haemoptysis, melaena, excessive menstrual bleeding, etc.
- Patients must immediately inform their GP if they have excessive or prolonged bleeding.
- Patients should carry anticoagulant booklets for the recording of INR results and anticoagulation dose. Copies of the St. James's Hospital Warfarin booklet are available from the centre.

INITIATING THERAPY

The usual induction dose is 10mg for 2 days. A prothrombin time should be measured prior to therapy to assess liver function. Ideally the dose should be given at the same time each day, usually between 5-7 pm, and the INR measured 16 hours later, i.e. between 9-11 am.⁵

The induction dose should be reduced in the following situations; prolonged prothrombin time, abnormal liver function tests, congestive cardiac failure, parental feeding, below average body weight, concurrent interacting drug therapy and in the elderly (over 80 years).

MONITORING THERAPY

This is done by measurement of the International Normalised Ratio (INR). This is a ratio of the patient's prothrombin time to an international standard.

MAINTENANCE DOSE

For the majority of patients it will fall between 3mg and 9mg daily. However responses may vary widely between patients and in the same patient over a period of treatment. Very occasionally patients may show hereditary resistance to warfarin and require large doses of warfarin or may respond more effectively to a different type of oral anticoagulant.⁶

TARGET INR RANGES³

The optimal intensity of oral anticoagulation remains uncertain; the table below contains suggested INR ranges for various clinical states.

INR	Clinical state
2.0 - 2.5	Prophylaxis of deep vein thrombosis including surgery on high risk patients (2.0-3.0 for hip surgery and fractured femur operations)
2.0 - 3.0	Treatment of deep vein thrombosis Pulmonary embolism Prevention of venous thromboembolism in myocardial infarction Mitral stenosis with embolism Transient ischaemic attacks Atrial fibrillation Tissue prosthetic heart valves
3.0 - 4.5	Recurrent deep vein thrombosis and pulmonary embolism i.e. recurrent even when in the range of 2-3. Arterial disease including myocardial infarction Mechanical prosthetic heart valves

DURATION OF THERAPY

Determining optimal duration of therapy remains difficult because not all cases of venous thromboembolism are the same and the risk of recurrence varies with different subgroups of patients.^{7,8}

The natural course of venous thromboembolism is one of recurrence, most commonly in the ipsilateral leg or with pulmonary embolism. The risk of recurrence is of the order of 22% in the first four weeks after discharge. Oral anticoagulation reduces this risk to 4%.^{8,9}

Recurrence rates are lower in patients with temporary risk factors (e.g. surgery, trauma, temporary immobilisation, travel, oestrogen treatment, infection, baker's cyst and pregnancy) than those with permanent risk factors (e.g. idiopathic venous thromboembolism, atrial fibrillation, malignancy, inherited coagulation disorder or presence of lupus antibodies.).^{8,9}

Patient with a permanent risk factor should be anticoagulated for at least six months after an unprovoked episode of venous thromboembolism and in certain cases longer term or indefinite treatment should be considered. Patients with temporary or reversible risk factors do not require long-term anticoagulation and on available evidence oral anticoagulation may be stopped after 6-12 weeks of treatment.^{8,9}

FREQUENCY OF INR MEASUREMENT

Initially the INR should be checked daily or on alternate days after commencing therapy. After hospital discharge weekly INR estimation is advised for 4-6 weeks. Thereafter, measurement can be extended to every 8 weeks if compliance and control are satisfactory. ⁵ Changes in the patient's medical condition such as heart disease, thyroid status or drug therapy may alter anticoagulant control and require more frequent monitoring.³

SURGICAL PROCEDURES

For minor operations studies have shown that oral anticoagulants may be continued with only a minimal risk of bleeding.¹⁰

The European Society of Cardiology suggest that for extensive surgical procedures an INR of 2.0 or below is required. This may require discontinuation of oral anticoagulants for several days with the patient maintained on heparin before and after elective surgery.

ADVERSE REACTIONS

Bleeding is the most important complication of oral anticoagulation therapy. Other side effects include skin necrosis (usually occurs on days 3 - 8 of therapy), alopecia, purple toes and hypersensitivity reactions.

BLEEDING

Bleeding is more likely in patients with cerebrovascular disease and venous thrombo-embolism.¹¹ Anticoagulant bleeding most often affects the GI tract, urinary tract, soft tissues and oropharynx. Intra-cranial bleeding accounts for only 2% of anticoagulant related bleeding.¹

Factors shown to associated with a higher risk of bleeding during long term anticoagulant therapy include;

- History of past GIT bleeding¹²
- Atrial fibrillation¹²
- Presence of one of more of three comorbid conditions; Recent myocardial infarction, renal insufficiency or severe Anaemia.¹²
- History of stroke¹²
- Variability in the INR

The risk of bleeding during warfarin therapy is highest during the first month and may be greater with age over 65 years although there are conflicting reports as to the effect of increasing age.¹¹ Bleeding rates are higher with higher intensity therapy and direct related to length of anticoagulant therapy.¹¹

Patients who bleed with an INR in the therapeutic range may have an underlying pathological lesion as the cause of bleeding (in particular a GIT or Renal lesion) which should be investigated.¹³

PROBLEMS WITH ORAL ANTICOAGULANT TREATMENT³

- 1 a) *Life threatening haemorrhage* - Refer to hospital.
Immediately give 5mg phytomenadione (vitamin K.) by slow intravenous injection and a concentrate of factor II, IX, X, (with factor VII concentrate if available) or if unavailable fresh frozen plasma. **Phytomenadione takes several hours to act and large doses may reduce the response to resumed therapy with anticoagulants for a week or more.**
b) *Less severe haemorrhage such as haematuria and epistaxis*
Withhold warfarin for one or more days, check INR, and consider giving phytomenadione 500 microgram -2.0mg by slow intravenous injection. Consider hospital referral.
- 2 *INR of greater than 4.5 with out haemorrhage*
Withdrawal warfarin for one or two days, then review. If the INR is greater than 7 consider the use of Phytomenadione (vitamin K.) and hospital referral.
- 3 *Unexpected bleeding at therapeutic levels.*
Investigate possibility of underlying cause such as unsuspected renal or alimentary tract disease and check INR.

DRUG INTERACTIONS^{2,3,14,15} *Note - this is not a complete list* (List is in alphabetical order)

Drugs which increase warfarin's anticoagulant effect.	Drugs which decrease warfarin's anticoagulant effect.
Alcohol (large amounts) Amiodarone Aspirin & other NSAIDS (due to Anti platelet effect. 2nd + 3rd generation cephalosporins Cimetidine Ciprofloxacin Co-Trimoxazole Erythromycin Fluconazole Ketoconazole Metronidazole SSRI'S Thyroxine	Anticonvulsant: Carbamazepine Phenobarbitone Broad spectrum antibiotics Cholestyramine Griseofulvin Rifampicin

WHO SHOULD MANAGE ANTICOAGULATION CONTROL:

Opinion is divided as to whether anticoagulation clinics should be in a primary care or hospital based setting. GP monitoring may offer better knowledge of concomitant disease and drug therapy and greater continuity of care. Complex cases with ongoing hospital care will continue with hospital monitoring. The anticoagulant record card provides for shared care and with an increasing number of patients on warfarin the contribution of G.P.'s is likely to increase.

REFERENCES

1. *A.M.J. Medicine* 1993;Vol 95; 316 - 327.
2. *N. Eng. J. Med* 1991; 324; 1865-75.
3. *J. Clin. Pathology* 1990; Vol 43; 177 - 183.
4. *Medicines Resource Bulletin*. Issue 31 1996.
5. *Drug Ther Bulletin* 1992; 30; 77 - 80.
6. *Arch. Intern Med.* 1985; 145;499 - 501.
7. *Lancet* 1992; 340; 873 - 876.
8. *N. Eng. J. Medicine* 1995; vol 332; 1710 - 1711.
9. *B.M.J.* 1995; 311; 700-701.
10. *Br. J. Surg.* 1995; 82; 577 - 578.
11. *Lancet* 1996; vol 346; 423 - 428.
12. *A.M.J. Medicine* 1989; Vol87; 144.
13. *Chest* 1992; 102; 352 - 362.
14. British National Formulary No. 32, 1996 Appendix 1; Drug Interactions: 566 - 567.
15. *Martindale* 31st Edition, 1996; 965 -972.