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Welsh Medicines Resource Centre
Canolfan Adnoddau Moddion Cymru

Monitoring anticoagulant therapy in primary care

In Wales, more than 600,000 prescriptions for oral anticoagulants were dispensed in primary care during 2006.[1] Warfarin, the agent of choice, accounted for 99.7% of these prescriptions. The most common indications for anticoagulant therapy are: prophylaxis of embolus in atrial fibrillation (AF), treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolus (PE), and prophylaxis of embolus in patients with mechanical heart valves.[2]

This Bulletin considers issues that should be addressed by anticoagulant monitoring services in primary care. It updates the previous WeMeReC Bulletin on this topic, and precedes further guidance expected from the National Patient Safety Agency (NPSA).

Monitoring anticoagulant therapy

All of the available oral anticoagulants (warfarin, acenocoumarol, and phenindione) have narrow therapeutic indices; monitoring is essential to ensure safety and effectiveness. Patient sensitivity to anticoagulants is variable and concomitant administration of many other drugs, as well as foods, food supplements, alcohol, and intercurrent illness can cause variations in the degree of anticoagulation – sometimes with catastrophic results. The **International Normalised Ratio (INR)**, a standardised measure used for reporting prothrombin time, is the recognised standard for monitoring warfarin therapy.

The patient partnership

Patient education and co-operation are vital during anticoagulation. A lack of knowledge about therapy may compromise a patient's safety resulting in: under- or over-anticoagulation; concurrent self-administration of drugs that may interfere with treatment; a failure to recognise problems, such as bleeding, early; and the inability to manage missed doses. Broader educational issues such as a patient's literacy and numeracy skills can also affect their anticoagulation control.[3] The level of additional support needed must be individually assessed, but all patients should receive and be counselled on the use of a patient-held record ('yellow book' – see *Resources*, page 6).

Summary

♦ An anticoagulant clinic should follow national guidelines with input from the local haematology department.

♦ Patient education and co-operation are vital during warfarin therapy to minimise risk.

♦ Warfarin doses and the frequency of INR measurement should be individualised.

♦ Any medicine should be considered to potentially interact with warfarin unless it is known otherwise.

♦ Bleeding, the most common adverse effect of warfarin therapy, should be investigated whether or not the INR is raised.

Guidelines for monitoring therapy

The **British Committee for Standards in Haematology (BCSH)** recommends:[4,5]

♦ INR targets (see Table 1)
♦ treatment durations for different indications.

It also suggests:

♦ intervals between INR measurements
♦ arrangements for managing services.

Table 1 Suggested INRs by indication[4,5]

INR	Indication
2.5	PE, proximal DVT, calf vein thrombosis, recurrence of venous thromboembolism when no longer receiving warfarin (or when on warfarin but with a sub-therapeutic INR), AF
3.5	Recurrence of venous thromboembolism when on warfarin with a therapeutic INR

Requirements for other indications, such as mechanical prosthetic heart valves, differ and are included in the full BCSH guidelines.

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Initiating therapy

Dose selection and adjustment needs to be specific to each patient. The baseline INR should always be measured before initiating therapy; modifications to the loading dose may be necessary if the results are abnormal. Some patients may be particularly sensitive to the effects of warfarin, including: the elderly; those with liver disease, cardiac failure, or those who are immediately post-operative; and patients on concomitant medicines that are known to potentiate the effects of warfarin.

During induction and initial stabilisation of patients on warfarin, clinics should be able to accommodate frequent INR measurements. A variable, tailored loading schedule based on individual INR results is widely used in secondary care (see Table 2). Professionals working in primary care clinics may need to refer to this schedule for guidance on the treatment of recently discharged patients.

Several other initiation schedules have been studied and three of these are included in the updated BCSH guidelines.[4] All three schedules are based on studies that use smaller loading doses of warfarin: one used 2 mg for two weeks,[6] the second used 3 mg for one week,[7] and the third used 5 mg for three days.[8] Although these schedules allow for less frequent INR measurement, the time to reach the target INR takes longer than with the use of the tailored approach shown in Table 2. These low-dose schedules are suitable when daily INR measurement is not possible and the patient does not require immediate anticoagulation.

Continuing therapy

Duration of therapy is determined by the condition that is being treated and other patient-specific factors, and should be noted by the referring specialist. The duration of treatment may vary from 6 weeks to 6 months or more for a first venous thrombosis, or could be life-long for recurrent thrombosis or cardiac indications.[4,5]

The daily maintenance dose of warfarin is usually in the range of 3-9 mg taken at the same time each day.[9] Lower or higher doses, however, are not uncommon.

Target INRs are now advocated in preference to ranges, with a result within 0.5 units of the target generally deemed as satisfactory.[5] When the INR deviates beyond this, adjustments in the maintenance dose should be made in small increments. An adjustment of 5-20% of the weekly dose usually results in a measurable change in the INR.

After induction and initial stabilisation on warfarin, the INR will usually dictate the frequency of monitoring. Weekly monitoring is advised until control is stable. The time between measurements can then be increased if compliance and control are satisfactory. The time between measurements should not exceed 12 weeks (6 weeks for patients with prosthetic heart valves). More frequent monitoring may be necessary as medical circumstances dictate (for example, changes in condition, medication, diet, etc. – see Table 3, page 4).

Stopping therapy

Concern about a 'rebound hypercoagulable state' after stopping warfarin has led to questions about whether therapy should be tapered off gradually. Evidence now suggests that there is no need for a gradual withdrawal of anticoagulants. Warfarin can be withdrawn abruptly when treatment is complete.[4]

Table 2 Suggested warfarin loading schedule[10]

Day	INR	Daily warfarin dose (mg)	Day	INR	Predicted maintenance dose (mg)
One	< 1.4	10	Four	< 1.4	> 8
Two	< 1.8	10		1.4	8
	1.8	1		1.5	7.5
	> 1.8	0.5		1.6-1.7	7
				1.8	6.5
Three	< 2.0	10		1.9	6
	2.0-2.1	5		2.0-2.1	5.5
	2.2-2.3	4.5		2.2-2.3	5
	2.4-2.5	4		2.4-2.6	4.5
	2.6-2.7	3.5		2.7-3.0	4
	2.8-2.9	3		3.1-3.5	3.5
	3.0-3.1	2.5		3.6-4.0	3
	3.2-3.3	2		4.1-4.5	Miss next day's dose then give 2 mg
	3.4	1.5		> 4.5	Miss 2 days' doses then give 1 mg
	3.5	1			
	3.6-4.0	0.5			
	> 4.0	0			

Where to monitor therapy

For many patients, providing supervision of anticoagulation in primary care has the advantage of combining improved access with continuity of care. Where near-patient testing is used (rather than blood samples being sent away for analysis), on-the-spot decisions regarding any necessary dose changes can be made and immediately communicated to the patient in person.

With the advent of home testing devices, patient self-monitoring has also become an option in some areas. Patients monitoring their therapy at home can either adjust their treatment according to a predetermined dosing schedule, or call their clinic to receive appropriate advice. Current evidence for self-monitoring suggests that these approaches may be appropriate for some motivated patients, if underpinned by structured training and follow-up.[4] Further data on clinical and cost outcomes are needed before widespread implementation of patient self-monitoring can be recommended.

Minimising risk with anticoagulants

Oral anticoagulants are one of the three classes of drugs most frequently associated with fatal medication errors in primary care. They are included in the Department of Health (DH) report, *Building a safer NHS for patients: improving medication safety,*[11] as medicines that require special safety controls. In the report, the DH recommends that wherever possible, prescribers should use computerised decision support software. Such systems can be used to standardise doses, to alert prescribers when treatment should be discontinued, and to identify non-attendees at INR clinics. One of the recommendations made by the BCSH, however, is that there should be a facility to over-ride the decisions made by the software.[5] If computer-generated dose schedules are used, they should always be checked by experienced personnel.

All patients should be regularly assessed for the risks and benefits of continuing therapy. Those considered to be at greater risk, such as the elderly, should be reassessed more frequently.

Requirements for primary care clinics

It is necessary to involve local haematology departments in the planning and implementation of anticoagulant clinics. The methods chosen for blood sampling and analysis, and their quality assurance, are critical. It is also important to ensure the seamless care of patients between hospital and community settings.

The BCSH recommends that responsibilities and organisational procedures for an anticoagulant service should be documented. There should be a lead clinician in charge of the service, including the training of personnel.[5] Training needs will vary with profession but an understanding of anticoagulation and the pharmacokinetics and pharmacodynamics of warfarin is essential. Experience should be gained through practice at established clinics. Dedicated records should be kept for warfarin therapy, including indication, INR target, treatment duration, doses, and concurrent medicines. The initial referral form, other correspondence, and patient details (including phone number) should also be kept. The records should be checked at each visit and kept current.

To reduce risks and protect patients, special attention should be paid to the following:[2 5,12]

♦ Establishing work competencies for staff and provide training for those who prescribe and dispense anticoagulants, and monitor therapy.

♦ Initiating therapy where indicated.

♦ Documenting reasons and plans for treatment.

♦ Prescribing correct (safe and adequate) doses.

♦ Carefully considering the co-prescribing and monitoring of non-steroidal anti-inflammatory drugs (NSAIDs) and other interacting medicines.

♦ Making adequate arrangements for, and communicating about, hospital discharges.

♦ Providing sufficient support to vulnerable groups of patients and to all patients during the first three months of therapy.

♦ Checking repeat prescribing and dispensing.

♦ Standardising supply and use of different strengths of anticoagulants and ensuring that the patient is confident with these.

♦ Providing appropriate (consider language) and up-to-date verbal and patient-held information.

♦ Conducting clinical audit and responding to findings (see *Resources,* page 6).

Medicines that interact with warfarin

The majority of medicines that interact with warfarin potentiate its effect, resulting in an increased risk of haemorrhage. Of particular significance is the interaction between warfarin and NSAIDs which is a potential cause of serious bleeding events, particularly in elderly patients. Despite this, prescribing of NSAIDs to elderly patients is not lower in those on warfarin compared with those who are not.[13] Using a selective COX-2 inhibitor instead of an NSAID confers no advantage in terms of bleeding events.[14]

Corticosteroids have also been implicated in interactions with warfarin, causing either an enhanced or reduced anticoagulant effect. Evidence suggests that high-dose corticosteroids cause an enhanced effect.[9,15] The use of corticosteroids and NSAIDs together has been shown to lead to a 15-fold increase in the risk of peptic ulcer compared with non-use of either drug.[16] It would therefore seem prudent to avoid the use of this regimen with concomitant warfarin therapy where possible.

Common experience suggests that INRs can sometimes be altered by broad-spectrum penicillins. A variety of other widely used antibiotics can also affect INR, including: trimethoprim, ciprofloxacin, metronidazole, and the macrolides (for example, erythromycin, clarithromycin), cephalosporins, tetracyclines, and sulphonamides.[9]

Patients and clinic personnel should also be alert to the potential for interactions between warfarin and **over-the-counter medicines**, including herbal remedies and food supplements. Known, potentially serious, interactions that increase anticoagulation have been reported between warfarin and fluconazole, NSAIDs and salicylates (oral and topical), and miconazole oral gel. Glucosamine, and large amounts of cranberry juice, may have the same effect.[9,17] St John's Wort also interacts with warfarin but decreases the anticoagulant effect.[17] See Appendix 1 of the British National Formulary (BNF) for a more complete list of interacting drugs.

Any medicine should be considered to potentially interact with warfarin unless it is known otherwise.

When introducing short courses (<5 days) of a new drug, adjusting the oral anticoagulant schedule is not essential but a slight dose reduction, or the omission of a single dose, could be recommended if a known potentiator is prescribed. If an interacting drug is prescribed for more than 5 days the INR should be checked 5-7 days after its initiation and the warfarin dose adjusted on the basis of the result.[5] If the interacting drug is subsequently withdrawn, care must be taken to readjust the warfarin dose accordingly. The effect of some drugs (for example, amiodarone) persists for some time after cessation.

Table 3 Examples of factors affecting anticoagulation

Potentiating factors	Mechanism	Advice/comment
Diarrhoea	Alterations in intestinal flora and ↓ vitamin K absorption	Diarrhoea may possibly also reduce the absorption of warfarin.
Febrile illness	↑ catabolism of clotting factors	As for all potentiating factors, patients should report bruising or bleeding problems to their doctor.
Exacerbation of CHF, or hepatic congestion	↓ metabolism of warfarin	
Hyperthyroidism	↑ catabolism of clotting factors	Monitor INR frequently in patients with changing thyroid function.
Alcohol (acute)*	↓ warfarin metabolism	Do not exceed moderate alcohol intake (1-2 units daily). Do not 'binge drink'.
Antagonising factors	Mechanism	Advice/comment
Hypothyroidism	↓ catabolism of clotting factors	Monitor INR frequently in patients with changing thyroid function.
Diet	↑ vitamin K consumption, e.g. some dietary supplements, and green vegetables	Avoid crash diets and significant changes in consumption of dietary vitamin K. Report any significant changes to the anticoagulant clinic.
Alcohol (chronic)*	↑ warfarin metabolism	Dosage requirements may be higher in heavy drinkers.

* In patients with established liver damage dose requirements are likely to be lower as the metabolism of warfarin is decreased.

Adverse effects

The main adverse effect of warfarin is haemorrhage (see Table 4 for a summary of management). Main sites of bleeding are the gastrointestinal (GI) tract, urinary tract, and the soft tissues.

Factors that put patients at high-risk of bleeding with warfarin include:[18]

♦ age >75 years

♦ history of uncontrolled hypertension

♦ alcohol excess and/or liver disease

♦ poor drug compliance and clinic attendance

♦ bleeding lesions (especially GI blood loss or recent cerebral haemorrhage)

♦ bleeding tendency (due to coagulation defects)

♦ concomitant use of interacting medicines

♦ instability of INR control and INR >3.

Older patients are at greater risk of bleeding because ageing is associated with a higher prevalence of chronic diseases, an increased incidence of adverse drug reactions, and an increased sensitivity to warfarin. The risk of bleeding can be reduced by carefully selecting and educating patients, and by maintaining the target INR for the recommended duration.

Managing raised INRs and bleeding[5]

Major bleeding
Stop warfarin and admit patient to hospital.

INR > 8.0 (with minor or no bleeding)
Stop warfarin.
If no risk factors for bleeding, restart when INR<5.0.
If risk factors for bleeding present, give vitamin K_1 0.5 - 2.5mg orally using IV preparation (*Konakion MM®*) for partial reversal. Higher doses are required for full reversal.[9]

INR 6.0 - 8.0 (with minor or no bleeding)
Stop warfarin, restart when INR<5.0.

INR < 6.0 (but > 0.5 units above target)
Stop or reduce warfarin, restart when INR<5.0.

Unexpected bleeding at therapeutic levels
Always investigate possibility of underlying cause (e.g. unsuspected renal or GI tract pathology).

Contraindications to warfarin include; peptic ulcer, severe hypertension, bacterial endocarditis, and pregnancy.[9] The Royal College of Obstetricians and Gynaecologists has published guidelines on the assessment of risk factors and the treatment and prophylaxis of thromboembolism during and after pregnancy (see *Resources*, page 6).

Some pharmacology…

Mechanism of action and pharmacokinetics

Oral anticoagulants antagonise vitamin K, reducing the vitamin K-dependent synthesis of clotting factors II, VII, IX and X, as well as the antithrombotic factors, proteins C and S. The onset of action is delayed until existing clotting factors have been catabolised. The half-lives of the clotting factors range from 6 - 60 hours and a therapeutic effect is normally seen at 24 hours. The peak effect may not be seen for 48 - 72 hours after a dose and the overall effect may last for up to 5 days.

Warfarin has a half-life of about 35 hours and it can take about a week of dosing to reach steady state. This, together with the delay in the clearance of clotting factors and patient variability, can affect the initial stabilisation of patients on warfarin.

Metabolism and interactions

Warfarin consists of an equal mixture of two enantiomers, *R*- and *S*-warfarin, with the *S*-form appearing to be at least five times more potent than the *R*-form. The enantiomers are metabolised stereo-specifically in the liver by the cytochrome *P*-450 system. This may be important when looking at interactions that affect the clearance of warfarin.

A number of drugs are known to inhibit the metabolism of either, or both, of the enantiomers.[19] It follows that if an interacting drug specifically reduces the metabolism of *S*-warfarin, a large increase in INR may occur within a short space of time. In contrast, a small number of drugs may increase warfarin clearance and so lead to a decrease in anticoagulation. Other mechanisms of interaction include interference with clotting factors, platelet aggregation, and vitamin K absorption.[15]

Resources

The BCSH guidelines, including guidance for clinical audit criteria, safety indicators, and the management of anticoagulation in the peri-operative period can be accessed via:
www.bcshguidelines.com

The NPSA risk assessment of anticoagulant therapy can be accessed via:
www.npsa.nhs.uk

Your local Medicines Information Centre can be contacted for specific enquiries regarding anticoagulation, especially for interactions with medicines/complementary therapies not included in the BNF. Details via:
www.wmic.wales.nhs.uk

The Royal College of Obstetricians and Gynaecologists guidelines:
Thromboprophylaxis during pregnancy, labour and after vaginal delivery - January 2004 can be found at:
www.rcog.org.uk/index.asp?pageID=535
Thromboembolic disease in pregnancy and the puerperium: acute management - April 2001 can be found at:
www.rcog.org.uk/index.asp?pageID=533

National Public Health Service for Wales: Anticoagulation Monitoring - National Enhanced Service:
www.wales.nhs.uk/sites3/page.cfm?orgid=719&pid=23548

The patient-held record (yellow book) can be ordered from:
Astron, The Causeway, Oldham Broadway, Business Park, Chadderton, Oldham, OL9 9XD
Tel: (0161) 683 2376

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