Managing warfarin therapy in the community

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SYNOPSIS

Warfarin is the most widely used oral anticoagulant in Australia. Although it can prevent thrombosis, it can cause life-threatening haemorrhages. Patients taking warfarin should have their INR measured regularly. More frequent tests are needed when patients start, stop or alter the dose of their other medications. Educating the patients about warfarin helps them to take their treatment correctly. They should report any abnormal bleeding and have their INR measured. A very high INR is an indication for admission to hospital to have the effects of warfarin controlled.

Index words: anticoagulation, coagulation, thrombosis.

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Introduction

Warfarin is one of the commonest causes of death related to prescription drugs, but when used appropriately it is one of the most beneficial drugs. As the population ages and more trials show its benefits, more and older patients will be started on warfarin. Its pharmacology is complicated and many factors need to be considered in the optimal management of each patient.

Risks and benefits of warfarin

There are many indications for warfarin therapy (Table 1). The decision to start warfarin depends on an assessment of each patient's balance between the harmful effects and the benefits of anticoagulation.

The major adverse effect of warfarin is an increased bleeding tendency and many factors can increase the risk (Table 2).[1] A patient's risk of bleeding is greatest in the first few months after starting warfarin. Bleeding complications occur in 3–10% of patients on warfarin per year, but most bleeds are minor. Although the bleeding risk increases as the INR (International Normalised Ratio) increases, 50% of bleeding episodes occur while the INR is less than 4.0.

Age is one of the strongest risk factors for bleeding. In one study, the annual risk of major bleeding was 2.9% for patients older than 70 years, while no major bleeds occurred in patients under

Table 1

The common indications for warfarin therapy

Supported with good evidence

- prosthetic valve replacement
- deep vein thrombosis within the last three months
- pulmonary embolism within the last six months
- recurrent deep vein thrombosis or pulmonary embolism
- atrial fibrillation associated with valvular heart disease
- atrial fibrillation without structural heart disease in patients >50 years old
- embolic stroke

Supported but limited evidence

- congestive heart failure or dilated cardiomyopathy

Little or no supporting evidence

- non-embolic cerebrovascular disease
- peripheral vascular disease

Table 2

Risk factors for major bleeding in patients on warfarin

Marked increase in risk

- age >70 years old
- bleeding disorder
- gastrointestinal haemorrhage within the last 18 months
- previous stroke
- liver disease
- history of falls

Moderate increase in risk

- age 60–70 years
- chronic renal failure
- change in interacting medications (see Table 4)
- change in, or poor, nutrition
- first three months of warfarin therapy
- large fluctuations in INR

50 years old.[2] Bleeding in this report was called 'major' if it was fatal, was intracranial, retroperitoneal or involved a joint, required surgery, led to a haemoglobin fall of 2 g/dL or more, and/or required the transfusion of two or more units of blood.

Warfarin in pregnancy is teratogenic and causes peripartum bleeding in mother and child, so it is generally contraindicated in pregnancy. There may be a place for mid-trimester warfarin in pregnant women with prosthetic heart valves, but this choice should be made only after a full discussion of the implications with the patient. Unfractionated heparin and low molecular weight heparin are alternatives that do not cross the placenta.

Patient education

Patients who have a poor understanding of the indications and potential adverse effects are more likely to be non-compliant than those who receive education about warfarin.[3] Patients should be encouraged to:

- report any signs of bleeding while on warfarin
- have more frequent measurements of their INR when starting or stopping other medications, either prescribed or complementary
- keep a written record of INR results and warfarin dosage
- remain with one or other of the currently available brands of warfarin (Coumadin or Marevan), as these have not been formally shown to be bioequivalent and are therefore not interchangeable.

Booklets aimed at patient education are available from all pharmacies. These are a useful supplement to the doctor's advice.

Women of childbearing age should be informed of the potential dangers of warfarin in pregnancy. Pre-conception counselling is needed for women on long-term treatment.

Trials of patient-based self-monitoring and dose-adjustment of warfarin therapy are under way, but currently this cannot be recommended.

Starting warfarin therapy

Patients with acute thromboembolic events, such as deep vein thrombosis, pulmonary embolism or embolic stroke, should be given heparin or low molecular weight heparin when starting warfarin. The heparin or low molecular weight heparin can be ceased after a minimum period of five days of combined therapy with warfarin and after the INR has been in the therapeutic range for 48 hours. Patients at less immediate risk, such as patients in stable atrial fibrillation without embolic events, may be safely started on warfarin without concurrent heparin.

Several trials have shown that low dose induction regimens cause fewer episodes of over-anticoagulation, with only minimal delay in the time to achieve the target INR. One protocol, validated specifically in elderly patients, is given in Table 3.[4] Loading regimens of 5 mg warfarin per day in all patients have also been reported.[5] Previously, a modified Fennerty's protocol, using loading doses of 10 mg, 10 mg and 5 mg on the first three days, has been the most commonly used nomogram for starting warfarin. However, this protocol can lead to significant over-anticoagulation, particularly in the elderly.[4] With all induction protocols, a baseline INR is measured before starting warfarin, and the INR is measured each day until doses are stabilised.

Maintaining warfarin therapy

The target INR varies for different clinical situations.[6] For patients with mechanical prosthetic heart valves, the target INR is usually 2.5–3.5. For almost all other conditions, including deep vein thrombosis and pulmonary embolism, atrial fibrillation and tissue valve replacements, the target INR is usually 2.0–3.0. Patients with recurrent thromboembolic events while anticoagulated, and patients with cancer or antiphospholipid syndrome may benefit from a higher INR, but this approach should be undertaken with specialist advice.

The frequency of monitoring INR once the dose is stabilised should be determined by the clinical situation. Initially, patients will require a few tests each week, but this can be gradually decreased to once a week or once a fortnight if the INR is stable. Patients who have a very stable INR, no interacting medications and low bleeding risk, may only need to have a test once every four to six weeks.

Many hospitals have anticoagulation clinics for managing patients on warfarin, although most patients can be safely managed in the community. However, clinical trials suggest that patients managed at an anticoagulant clinic spend more time with a therapeutic INR and have a lower rate of major haemorrhage, compared to 'best usual care'.[7] Patients most likely to benefit from anticoagulation clinics include those with comorbidities, those with unstable INRs and those very sensitive to warfarin (requiring daily doses of 1 mg or less).

Table 3

A dosage schedule for starting warfarin therapy, validated in elderly patients

Day	*INR*	*Warfarin dose*
1	<1.4	10 mg
2	<1.8	5 mg
	1.8–2.0	1 mg
	>2.0	Hold
3	<2.0	5 mg
	2.0–2.5	4 mg
	2.6–2.9	3 mg
	3.0–3.2	2 mg
	3.3–3.5	1 mg
	>3.5	Hold
4	<1.4	10 mg
	1.4–1.5	7 mg
	1.6–1.7	6 mg
	1.8–1.9	5 mg
	2.0–2.3	4 mg
	2.4–3.0	3 mg
	3.1–3.2	2 mg
	3.3–3.5	1 mg
	>3.5	Hold

Dose adjustment after day 4 depends on clinical judgement based on the pattern of INR.
The table is slightly modified from the table in reference 4.

Table 4

Some of the important interactions of warfarin

Increased effect of warfarin (↑INR)	*Decreased effect of warfarin (↓INR)*	*Potentiate bleeding risk because of antiplatelet effect*	*Potentiate bleeding risk by effects on gastric mucosa*
Medications			
• Antibiotics (sulfonamides, erythromycin and other macrolides, metronidazole) • Antifungals (itraconazole, fluconazole, ketoconazole) • Amiodarone • Selective serotonin reuptake inhibitors (especially fluvoxamine, fluoxetine) • Cimetidine • Propylthiouracil • Quinine and quinidine • COX-2 inhibitors (celecoxib, rofecoxib)	• Antiepileptics (carbamazepine, phenytoin, barbiturates) • Rifampicin, rifabutin • Cholestyramine	• Aspirin • Non-steroidal anti-inflammatory drugs (except COX-2 inhibitors) • Clopidogrel • Dipyridamole • Tirofiban	• Aspirin • Non-steroidal anti-inflammatory drugs
Herbal medicines			
• Dong quai • Garlic • Papaya • St John's wort	• Ginseng		

Interactions with warfarin

Warfarin is particularly prone to interactions with other drugs, herbal medicines[8] and dietary factors (Table 4). Some interactions involve the cytochrome P450 system in the liver. Many interactions are unpredictable, so the INR should be tested more frequently after starting a new medication and similarly when stopping a medication or changing the dose. It takes about five days for enzyme induction to take place, so that an INR measured about one week after a change in medication should reflect any interaction. In one study, recent antibiotic use was the second greatest risk factor (after age) for over-anticoagulation.[9]

Alcohol in small to moderate amounts probably has little effect on warfarin metabolism. In heavy drinkers, however, factors such as increased falls, alcohol-induced gastritis, poor diet and poor compliance potentiate the risk of bleeding.

The amount of vitamin K in the diet partly determines the sensitivity to warfarin. A diet high in vitamin K reduces the response. This is important to consider in situations when diet changes, such as during illness, travel, fad diets, hospitalisation and postoperatively. Foods high in vitamin K include green tea, turnips, avocados, brussel sprouts, broccoli and green leafy vegetables (e.g. lettuce, cabbage). It takes a very large daily intake of 'greens' to influence the INR. In any case, a consistently sustained diet will minimise this potential source of fluctuating results.

Table 5

A protocol for managing over-anticoagulation[9]

No bleeding	
INR 4–5.9	Withhold warfarin and measure INR next day
INR 6–9	Vitamin K 1–2.5 mg subcutaneously or orally*
	Recheck INR next day
INR >9	Hospitalise
	Vitamin K 5 mg IV or subcutaneously*
	Fresh frozen plasma 2 Units. This may be given with a factor II, VII, IX concentrate †
	Recheck INR after 6–8 hours and then daily for 3 days
Moderate or severe bleeding	
INR >1.5	Vitamin K 5–10 mg intravenously
	Fresh frozen plasma 2 Units immediately
	Recheck INR after 6–8 hours and then daily for 3 days (may need further vitamin K if INR rises)

* The intravenous preparation may be given orally or subcutaneously with safety and efficacy. Not all community pharmacies have the intravenous formulation of vitamin K and it may be worth keeping a supply in the practice rooms. (Avoid intramuscular injections of vitamin K to prevent local injection site bleeding which also reduces bioavailability.)

† Fresh frozen plasma and concentrates of clotting factors are blood products and may carry a small risk of viral contamination.

Management of over-anticoagulation

Over-anticoagulation increases the risk of haemorrhage. The first step in managing this problem is to identify the cause. Common causes include starting or stopping an interacting medication, deteriorating liver function, and patient error (such as taking the wrong dose or confusing different strength tablets). Many of these causes are preventable.

The approach to a raised INR should be individualised, paying attention to the indication for the warfarin, the patient's risk of bleeding and whether it is safe to continue therapy at all. Some patients need to be admitted to hospital, while others just need to miss a dose of warfarin.

Guidelines for managing over-anticoagulation (Table 5) are based on the recently published recommendations from the Australasian Society of Thrombosis and Haemostasis.[10] The half-life of vitamin K is shorter than that of warfarin, so the INR may rebound 24–48 hours after giving vitamin K. The intravenous preparation of vitamin K can be administered orally or subcutaneously with equal efficacy, and these routes are usually safer and more convenient in patients who are not actively bleeding.

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REFERENCES

1. White RH, Beyth RJ, Zhou H, Romano PS. Major bleeding after hospitalization for deep-venous thrombosis. Am J Med 1999;107:414-24.
2. Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Lancet 1996;348:423-8.
3. Arnsten JH, Gelfand JM, Singer DE. Determinants of compliance with anticoagulation: A case-control study. Am J Med 1997;103:11-7.
4. Gedge J, Orme S, Hampton KK, Channer KS, Hendra TJ. A comparison of a low-dose warfarin induction regimen with the modified Fennerty regimen in elderly inpatients. Age Ageing 2000;29:31-4.
5. Harrison L, Johnston M, Massicotte MP, Crowther M, Moffat K, Hirsh J. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. Ann Intern Med 1997;126:133-6.
6. Fifth ACCP Consensus Conference on Antithrombotic Therapy. Chest 1998;114 Suppl 5:439S-769S.
7. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. Arch Intern Med 1998;158:1641-7.
8. Fugh-Berman A. Herb-drug interactions. Lancet 2000;355:134-8.
9. Panneerselvam S, Baglin C, Lefort W, Baglin T. Analysis of risk factors for over-anticoagulation in patients receiving long-term warfarin. Br J Haematol 1998;103:422-4.
10. Gallus AS, Baker RI, Chong BH, Ockelford PA, Street AM. Consensus guidelines for warfarin therapy. Recommendations from the Australasian Society of Thrombosis and Haemostasis. Med J Aust 2000;172:600-5.

Self-test questions

The following statements are either true or false (answers)

3. The risk of warfarin causing bleeding is the same in all age groups.
4. The INR of a patient taking warfarin may be altered by a change in diet.

Medicinal mishap

Hidden haemorrhage with warfarin

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Case

A 78-year-old man presented to hospital because his right leg felt clumsy and weak. On assessment he had slightly reduced muscle power and appeared to have suffered a right hemiparesis. Over the next four hours, his right side became weaker, although he was still able to flex and extend his right hip against gravity. His ECG showed that he was in sinus rhythm with a heart rate of 70 beats/minute. He was started on warfarin therapy as we presumed that he had a 'stroke in evolution'.

After 10 days of warfarin therapy, the man noticed that his weak right leg was 'twitching' and he felt generally unwell. He complained of cramps in his right leg which made the whole leg 'jump off the bed', involuntarily. A few hours later, he became hypotensive but remained conscious. Clinical examination revealed that he had developed painful spontaneous contractions of his right hip flexors (positive psoas sign). The INR at this time was 2.7.

A CT scan of the abdomen showed a large haemorrhage in the retroperitoneal space and surrounding the right psoas muscle. Anticoagulation was stopped, and clotting factors and vitamin K used to reverse the anticoagulant status. The man's symptoms gradually settled and with a short intensive rehabilitation program, he made a good functional recovery.

Comment

Occult bleeding due to warfarin therapy can present in many ways and requires a high index of clinical suspicion for prompt diagnosis. It can also occur when the INR is in the therapeutic range, especially in older people, although the risk of bleeding is clearly higher when the INR exceeds the specified upper limit. Haemorrhage into the retroperitoneal space does not cause classic abdominal signs such as peritonism. A positive psoas sign is caused by conditions which irritate the psoas muscle. Tenderness may also be elicited by stretching the psoas muscle by hip extension. Apart from haematoma, other causes of a positive psoas sign include appendicitis and retroperitoneal abscess.