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Clot prevention

Common questions about medications

Background
Warfarin is commonly used in a number of clinical settings. Given the difficulties in managing patients taking warfarin, several questions are usually raised by clinicians in relation to its use.

Objectives
This article addresses some of the clinical questions related to warfarin use.

Discussion
Routine genetic testing before warfarin initiation is not currently recommended. None of the new oral anticoagulants is marketed in Australia for long term therapy as warfarin substitutes. Strategies to prevent thrombosis associated with air travel are discussed and measures to minimise the risk of bleeding are highlighted.

Keywords: anticoagulants; venous thrombosis/prevention; warfarin

CPD

Clot prevention is a common clinical dilemma – what to do when, and how to balance risks and benefits.

Management of warfarinised patients is associated with difficulties due to a number of factors, such as the narrow therapeutic index of warfarin and the risk of developing serious haemorrhage in these patients. Due to such difficulties, issues such as whether a gene test could predict warfarin responses and whether warfarin could be replaced by less toxic drugs such as aspirin or even some of the new anticoagulant have been raised. Due to the frequent fluctuation in the International Normalised Ratio (INR) in some patients, clinicians are frequently asked to make management decisions when the INR is outside the therapeutic range. Moreover, doctors are always searching for strategies to minimise the bleeding risk in anticoagulated patients. Clinicians are further confronted with situations where appropriate clot prevention measures may be required in a range of settings such as in association with air travel or a lower limb immobilised in a plaster cast following an injury.

What is the current role of pharmacogenomic testing for warfarin?

One of the major problems with warfarinisation in clinical practice is the wide inter-individual variability in dosage requirement. Polymorphisms in two genes (vitamin K epoxide reductase complex 1 [VKORC1] and the cytochrome P450 2C9 [CYP2C9] enzyme) have been shown to explain some of this inter-individual variability.[1] VKORC1 is the target enzyme inhibited by warfarin resulting in interruption of the recycling of vitamin K in the liver. CYP2C9 is responsible for the metabolic clearance of S-warfarin, the more potent isomer of warfarin. Even though numerous different algorithms incorporating genetic testing have been developed in an attempt to predict warfarin dose requirements,[2] such algorithms have not been validated in the Australian context, and their use cannot be recommended for routine practice yet. It is important to stress that the genetic polymorphism does not explain all the variability in warfarin dose requirements. Other important factors include: age, dietary vitamin K intake, the presence of other comorbidities and interaction with other drugs.

Is there a role for the new anticoagulants?

Several anticoagulants have been developed recently.[3,4] Most of them inhibit either thrombin or clotting factor X. The majority of these new anticoagulants are administered parenterally, which limits their use in the general practice setting. Currently there are no new marketed oral anticoagulants which can be prescribed instead of warfarin for long term anticoagulation.

There are two oral agents (dabigatran and rivaroxaban) currently marketed for the prevention of venous thromboembolism (VTE) after joint replacement. These agents may become available for long term anticoagulation in the near future.

Dabigatran etexilate is a prodrug that is converted by a serum esterase to dabigatran, a potent direct thrombin inhibitor. In 2009, a large trial was published showing a head-to-head comparison between dabigatran versus warfarin in the setting of atrial fibrillation.[5] This trial showed that at a dose of 110 mg twice daily, the rates of stroke and systemic embolisation were similar between the two groups, with lower rates of haemorrhage in the dabigatran group. However, at a dose of 150 mg twice daily, dabigatran use was associated with lower rates of stroke and systemic embolisation compared to warfarin, while both groups had similar rates of major haemorrhage. There was a small but statistically significant increase in the rate of myocardial infarction in the higher dabigatran dose compared with warfarin.

The other significant side effect with dabigatran was dyspepsia, which may be related to the dabigatran coated pellets with a tartaric acid core, so designed to enhance its absorption. Importantly, there were no signs of increased hepatotoxicity with dabigatran.

Rivaroxaban is a direct factor Xa inhibitor.[6] This drug was tested against enoxaparin in the setting of knee and hip surgery and was shown to be more effective than enoxaparin without excess bleeding. Trials of rivaroxaban against warfarin in the setting of atrial fibrillation are ongoing,[7] however, as yet, there are no published trials showing equivalence of rivaroxaban and warfarin.

So, will warfarin be replaced by these newer oral anticoagulants in the near future? As yet, none of these newer oral agents is marketed in Australia for long term anticoagulation. One of the major advantages of the newer agents is the fact that regular monitoring of their anticoagulant effect is not required, unlike warfarin. In addition, it seems that a fixed dose may be used with the newer drugs. This 'one size fits all' concept does not apply to warfarin. This may also be the disadvantage of these newer agents, as there is no method to assess their anticoagulant effect, and at the time of marketing, it is unlikely that much will be known about their safety in specific populations (eg. the elderly). Furthermore, many of the newer agents are renally cleared, and little is known about appropriate dosing recommendations in different degrees of renal failure, unstable renal function, or during acute illness.

Another disadvantage of the newer agents is the lack of a reversal strategy, should a patient suffer from bleeding. This is in contrast to warfarin, which can be easily reversed with vitamin K and infusion of clotting factors. In addition, these agents, despite being effective, may provide less protection against cardiovascular disease as shown by the increased rate of myocardial infarction with dabigatran compared to warfarin.[5] Therefore, even though the newer agents will be more convenient to use for both doctors and patients, because of these safety concerns, their initial use should be limited to those groups for whom safety and efficacy have been demonstrated in clinical trials, rather than the wholesale conversion of patients from warfarin to these newer agents.

The INR is outside of the therapeutic range, how should this be managed?

The management of an INR that falls outside of the therapeutic range depends on a number of factors, such as the degree and direction of the deviation of the INR from the desired range, the indication for warfarinisation and whether there are complications due to the INR deviation (eg. bleeding).

In a patient with an INR below the therapeutic range, the management will depend on the indication for warfarin therapy, the degree of deviation of the INR from the target range which then determines the risk of a subtherapeutic INR. For example, if the INR is just below 2.0 in a patient with atrial fibrillation, the daily risk of a stroke or systemic embolisation is very small and therefore other than increasing the warfarin dose and continuing monitoring of the INR, no other action is required. This is in contrast to an INR below 1.5 in a patient with a recent pulmonary embolus where strong consideration should be given to coadministration of enoxaparin subcutaneously until the INR is corrected. Other cases should be managed on an individual basis.

In cases where the INR is supratherapeutic, the management will depend on the degree of deviation from the target range and whether the patient is bleeding or not. In an asymptomatic patient, minor deviations from the target INR (INR between 3.1 and 4.0) can be managed by reducing the warfarin dose. In cases of more significant deviations (for example, if the INR is between 4.0 and 5.0), consideration should be given to withholding warfarin and reinstituting the therapy when the INR falls back to the therapeutic range. It is recommended that all patients with an INR value of over 9.0 receive 2.5–5.0 mg of oral vitamin K.[8] Similarly, patients with an INR between 4.0 and 9.0 who are at high risk of bleeding (eg. those with history of bleeding peptic ulceration) should receive oral vitamin K.[8] In a bleeding patient, regardless of the INR value, warfarin should be withheld and its effects reversed through the use of vitamin K and infusion of clotting factors, unless the bleeding is minor and stops with simple first aid measures. If bleeding continues, hospital presentation is most appropriate.

In all cases, and particularly when the INR has been stable, the cause of any significant change in INR should be sought. Careful attention should be given to exploring recent changes in medications.

What can be done to minimise the risk of bleeding in patients on long term warfarin?

Taking warfarin is equivalent to managing a chronic disease, and its success can be improved by interventions shown to be important in successful chronic disease management such as patient education, self management, improvement in communication, and multidisciplinary care.

Frequently, practice nurses are involved in the management of anticoagulated patients and can enhance the education and communication required for successful anticoagulation. The education required for a warfarinised patient can be extensive, including details of the required monitoring, food, drug, disease interactions, lifestyle changes (eg. alcohol consumption), as well as the symptoms of signs of bleeding.

A Home Medicines Review[9] can be particularly useful in managing a patient anticoagulated with warfarin. In this program, an accredited pharmacist is funded to visit the patient in their own home to spend approximately 1 hour reviewing the patient's knowledge of warfarin, potential interactions with other medicines (prescribed and nonprescribed), the patient's medication management knowledge and practices, and their understanding of warfarinisation. A report is then generated for the referring GP as well as community pharmacist for follow up of any issues that require further monitoring.

Is aspirin effective in preventing VTE?

The Australian guidelines state that aspirin is at best weak in preventing VTE.[10] One also has to take into account the risk of haemorrhage associated with prolonged aspirin use. Given such information, use of aspirin to prevent VTE in medical patients (and certainly in immobile nursing home residents) cannot be recommended.

What strategies are effective in preventing VTE associated with air travel?

Recommendations regarding this issue have been made on the basis of a recent systematic review.[11] All air travellers should exercise their leg muscles and avoid dehydration. Travellers with no known risk factors for VTE have a risk similar to that of the general population: that further prophylactic measures are not required. In travellers with a higher risk of VTE (previous history of VTE, cancer, obesity, impaired mobility, thrombophilia or varicose veins) use of knee high graduated compression stockings, 15–30 mmHg at the ankle, have proven efficacy and should be recommended for flights longer than 6 hours. If compression stockings cannot be used, or if the risk of VTE is judged to be exceptionally high, low molecular weight heparin (LMWH) can be used. However, it should be kept in mind that LMWH has not been well studied in this setting. Aspirin should not be used for this indication.

Is VTE prophylaxis effective in patients with lower limb plaster cast immobilisation?

This question has been addressed in four prospective randomised studies.[12–15] The indications for the plaster cast included both soft tissue injuries such as Achilles tendon rupture as well as bony fractures. In all of the studies, a form of heparin (mostly a LMWH) was tested against placebo or no treatment. The outcome in all the studies was radiological VTE confirmed either at cast removal or within 1 week. Importantly, none of the studies included symptomatic or clinically relevant VTE episodes as an outcome. The incidence of radiological VTE in the placebo/no treatment groups ranged from 4.3–19.0% compared with 0–10% in the treatment groups. In three of the four studies the difference was statistically significant in favour of prophylaxis. Whether this translates to fewer VTE episodes is not clear from the available evidence, and given the known risks of heparinisation, it is not clear which patient populations should be targeted.

Key practice points

- There is currently no established role for routine genetic testing before warfarin initiation.
- None of the new anticoagulants are currently marketed in Australia for long term therapy.
- In a patient with significant haemorrhage, warfarin effect should be reversed in the hospital setting.
- Patient education and Home Medicine Reviews are important for risk minimisation in warfarinised patients.
- Use of aspirin to prevent VTE is not recommended.
- In addition to leg exercises and avoiding dehydration, compression stockings (or LMWH) can be used in patients with high VTE risk for flights longer than 6 hours. In low risk patients no added measures are required.
- LMWH reduces the risk of radiological VTE in patients with lower limb plaster casts. It is not clear from the available evidence whether this reduces the risk of clinical VTE as well.

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