

Leading Article

Control of warfarin therapy

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Warfarin has been established as the oral anticoagulant of choice for many years. It is preferred to other coumarin-type drugs because of its greater reliability in clinical practice, and it benefits many thousands of patients each year. Nonetheless, it is not without hazard and there must be very few doctors who have not experienced difficulties in controlling a patient's coagulation state.

Warfarin is indicated for prophylaxis of thrombi in patients with existing thrombi, such as deep venous thrombosis (DVT) or pulmonary embolism, or in those at high risk, such as atrial fibrillation, prolonged bed-rest, post-surgery.¹ The degree of anticoagulation required depends upon the condition being treated.² Prophylaxis for non-hip surgery requires an international normalized ratio (INR) of 2–2.5, hip surgery and treatment of DVT, pulmonary embolus or transient ischaemic attacks 2.0–3.0 and recurrent thrombosis, valvular or arterial disease 3.0–4.5. The standardization of assay procedures is vital but has been well covered elsewhere.³ Many minor surgical procedures can be adequately covered by the use of subcutaneous heparin and warfarin is in any case contraindicated in the first and third trimesters of pregnancy because of the high rate of fetal malformation and bleeding. It is also contraindicated in patients with bleeding diatheses, peptic ulceration, severe hypertension or endocarditis, although the presence of an artificial valve may over-ride the last contra-indication. In rare cases of allergy or intrinsic resistance to warfarin, phenindione can be used, as may intravenous or subcutaneous heparin.

The choice of an initial dose, and its conversion to a maintenance dose, is hampered by the delay in response (1–2 days), the wide variation between individuals and the lack of a close relationship between serum warfarin concentration and response. Several authors have published predictive schedules for dosing based on INR measurements in the first 2 days of treatment,^{4–6} but these have proved to be of only limited benefit and the most common method is still to 'try it and see'. In an otherwise healthy adult, a typical

regime would call for 9–10 mg daily for 3 days and then adjust the dose according to INR.⁶ Patients with thyrotoxicosis, liver impairment, heart failure, pre-existing high INR, or low body-weight should all be given lower doses (say, 9,6,6 mg) as should those over 80 years.

Careful control in an anticoagulant clinic is essential to good management and this can be achieved by practised doctors, nurses or pharmacists.⁷ Patient compliance is a major determinant of success, as are the numerous potential interactions with food and drugs. Some clinics try to improve compliance by using only one strength of warfarin tablet, thus simplifying the dosage instructions and reducing the risk of incorrect doses. Interactions may be divided into those that affect absorption, those that affect metabolism, those that affect protein-binding and those that affect coagulation directly or cause bleeding. Only the most important examples are given here, there are several good texts which may be consulted for details of others.^{8–11}

Absorption takes 2–4 hours, with a peak serum level at about 2 hours, and is generally faster after food. It is probably unaffected by antacids, despite some *in vitro* evidence to the contrary, but may be decreased by the use of laxatives. Cholestyramine resin or liquid paraffin can have variable effects on clotting because of effects on both warfarin and vitamin K. Special diets containing large amounts of vitamin K, or even a high intake of green vegetables, such as broccoli, can alter coagulation. Patients should be counselled to take their warfarin at the same time each day (the evening is usually convenient because it is easier to make dosage adjustments in the clinic with immediate effect) and either with or without food, but not sometimes with and sometimes without. To avoid problems associated with tablets sticking in the oesophagus, patients should swallow their tablets with a drink of water whilst standing or sitting upright.¹² Problems that may occur include oesophageal ulceration, a well-known complication for some other drugs but recently reported for the first time for warfarin by Loft *et al.*¹³ An unexpected difficulty caused by a pharyngeal pouch is reported by Ong and Slater in this issue¹⁴ and serves to illustrate the great vigilance

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Received: 14 March 1989

and detective work needed to control warfarin therapy.

Hepatic metabolism of warfarin by the mixed-function oxidases is enhanced by smoking, alcohol abuse, rifampicin, carbamazepine and barbiturates. Cimetidine, erythromycin, metronidazole and the quinolone antibiotics, such as ciprofloxacin and norfloxacin, inhibit hepatic enzyme function and potentiate the anticoagulant effect of warfarin. Isoniazid also potentiates warfarin but the mechanism is not clear. Drugs which decrease hepatic blood flow, such as propranolol, decrease warfarin metabolism, but to a lesser extent. Modest alcohol consumption does not appear to affect anticoagulation.¹⁵⁻¹⁶

Warfarin is extensively protein-bound in serum (about 99% to albumin) and is susceptible to displacement by other more-strongly bound drugs, such as phenylbutazone and sulphamethoxazole (in cotrimoxazole). The principal problem is not the existence of concomitant therapy, but the changes which occur when the other treatment is started or stopped. Only un-bound drug is active and when another protein-bound drug is introduced, the level of free warfarin rises as it is displaced from albumin. The anticoagulant effect is temporarily enhanced but the liver quickly metabolizes the free drug and the patient returns to a steady-state with a concentration of free warfarin similar to the former level, despite a decrease

in total serum level. The opposite happens when the interfering drug is stopped, there is a period of reduced anticoagulation followed by a return to the *status quo*. The time taken for full induction/inhibition of enzymes varies from 3–10 days but the time taken for the effect to wear off, once the interfering drug is stopped, is less well-documented. In the author's experience, it has occurred after 6–7 days.

Drugs which affect platelet function (dipyridamole, aspirin, sulphinpyrazone) should be used with caution with warfarin, or avoided completely. Patients should be counselled to avoid aspirin in home remedies for colds, headache etc. They should also avoid drugs which may cause bleeding by damaging the gastric mucosa. All non-steroidal anti-inflammatory agents, including ibuprofen which is available for purchase in pharmacies in UK, should be avoided or used under close medical supervision. Other drugs affect coagulation by a variety of mechanisms, warfarin being potentiated by amiodarone, quinine, quinidine, thyroxine and anabolic steroids. Spironolactone has been reported to antagonize warfarin, possibly by concentrating clotting factors.

There are many potential pitfalls in warfarin therapy, but most can be avoided by close monitoring with a reliable prothrombin time assay and intensive patient counselling. Warfarin remains a valuable drug but should be treated with respect.

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