A brief review of warfarin and the international normalised ratio

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Abstract
The use of warfarin anticoagulation is a common therapy that acts on the vitamin K dependent coagulation factors II, VII, IX and X by blocking gamma-carboxylation. Indications for warfarin therapy include deep vein thromboembolism prophylaxis and treatment, atrial fibrillation, pulmonary embolism and mechanical heart valve prostheses. Warfarin efficacy is monitored using the international normalised ratio (INR), which standardises laboratory results and allows meaningful interpretation of patient data between centres. This article provides a summary for medical students and highlights the importance of using INR in monitoring patients on warfarin.

As a medical student going through the clinical years of training it is interesting to finally confirm what our teaching staff have been telling us for years: that common things occur commonly. We will in our training encounter patients on warfarin anticoagulation on the wards, in outpatient clinics and in the community, therefore knowing something about the drug itself, some of the more important applications and how it is monitored makes good sense and good future clinical practice. Perhaps one of the more abstract concepts in managing patients on warfarin is the use of the INR.

Warfarin (warfarin sodium) is a medication that patients take for reasons ranging from deep venous thrombosis to atrial fibrillation. It remains one of the most effective forms of anticoagulation especially in the outpatient setting, due to the fact that it can be taken orally. Cynics would remind us that warfarin is also used in rodenticides giving rise to the colloquialism of 'rat-poison' when referring to warfarin.[1]

The INR is used to monitor warfarin efficacy in the context of a therapeutic range of anticoagulation for a given condition. The INR is the prothrombin time ratio using an international reference thromboplastin, which allows for greater standardisation in clinical practice.

This article briefly summarises the pharmacology and clinical uses of warfarin and how the international normalised ratio is used in monitoring patients on warfarin.

Pharmacokinetics and mode of action

Warfarin is a synthetic derivative of dicoumarol, which in turn is a derivative of bishydroxycoumarin, a toxic agent found in spoiled sweet clover silage. This toxin produces a deficiency of plasma prothrombin and subsequent haemorrhagic disease in cattle that died after de-horning or castration.[2]

Warfarin, like all its relatives, blocks the gamma-carboxylation of prothrombin, the vitamin K-dependant coagulation factors II, VII, IX and X and the endogenous anticoagulant proteins C and S. The result of this blockade is the production of incomplete molecules that are biologically inactive in the coagulation cascade.[3] Although warfarin prevents the reduction of vitamin K epoxide (relevant in synthesising factors II, VII, IX and X), natural mutation may occur in the responsible enzyme vitamin K epoxide reductase, which may give rise to genetic resistance to warfarin in humans and rats.

Warfarin is usually administered as a sodium salt and has 100% bioavailability. Over 99% of warfarin is bound to plasma albumin. A delay in the anticoagulation effect of warfarin is attributed to the time taken for degradation of coagulation factors already in circulation not affected by the drug. Half lives of the four vitamin K dependent factors II, VII, IX and X are 6, 24, 40 and 60 hours respectively. A larger loading dose, of up to 0.75 mg/kg warfarin, may accelerate the onset of action.

Therapeutic use

Patients requiring anticoagulation in hospital will tend to receive heparin in the first instance.[4] Given that warfarin may require 1-2 days to reach a therapeutic range of effect, the patient must be maintained on heparin until that goal is reached. Heparin may then be discontinued and the patient maintained on warfarin in anticipation of discharge. Herein lies the most important advantage of warfarin, especially in the outpatient setting – the ability for it to be taken orally.

The initial dose of warfarin varies from 5–10 mg daily until a therapeutic range is reached.[5] The therapeutic range should be monitored daily using the INR, although the prothrombin time is also used. The prothrombin time should be increased to reflect a level 25% that of normal clotting activity. The dose of warfarin used for maintenance is then adjusted using the prothrombin time and clinical judgment and experience.

Patients on warfarin anticoagulation may have a variety of conditions that require a higher degree of prevention from thromboembolism than aspirin or dipyrimadole can offer, and in some instances it may be used in conjunction with them. These conditions include post-myocardial infarction, mechanical heart valve prostheses of all types, atrial fibrillation, cardioembolic cerebral ischaemic events, venous thromboembolism, and rheumatic mitral valve disease. Each requires different levels of anticoagulation.[4 6] Patients with malignancies may also have hyper-coagulability as part of a neoplastic syndrome, and should also be considered for anticoagulation. The therapeutic INR for these conditions is set out in Table 1.

Warfarin readily crosses the placenta and is therefore generally contra-indicated during pregnancy.[6] Warfarin toxicity may arise from intentional or unintentional overdose, including ingestion of rodenticides. Clinically, common findings of excessive anticoagulation include ecchymoses, subconjunctival haemorrhage, epistaxis, vaginal bleeding, bleeding gums, and haematuria. Life-threatening complications include massive gastro-intestinal bleeding or intracranial haemorrhage.[7] Reversal of warfarin is achieved by administering intravenous vitamin K as 50 mg infusions, factor IX concentrates or fresh frozen plasma (FFP). Patients with higher than desired INR but no bleeding may only require a temporary cessation or lower warfarin dose.

The international normalised ratio

The therapeutic range for oral anticoagulation with warfarin is defined in terms of the INR. The method of performing prothrombin time (PT) was developed in the 1940s and involved adding calcium and thromboplastin to citrated patient blood.[3] Thromboplastin is derived from phospholipid-protein extracts such as brain, lung and placenta with rabbit brain thromboplastin the most commonly used. However, each laboratory prepared its own and, while effective reference ranges were established in their own institutions, there was huge variation between centres. Also, rabbit-derived thromboplastin was found to be less sensitive than human-derived thromboplastin.

As a result, patients in Europe were being anticoagulated to a lesser degree than their US counterparts, due to the sensitivity of the thromboplastin used in measuring PT. In other words, laboratories using a less sensitive thromboplastin were over-anticoagulating patients compared to those monitored using a more sensitive thromboplastin. The World Health Organization (WHO) in 1978 recommended a standardisation of PT and in 1983 published recommendations using an international standard thromboplastin, the basis of INR measurement.[8]

The INR attempts to normalise the PT test based on the sensitivity of different thromboplastins and is calculated as $INR = (PT / \text{mean normal PT })^{ISI}$ where the mean normal PT is the prothrombin time based on a mean of 20 fresh plasmas of healthy patients and ISI, the international sensitivity index.[8 9]

Using this WHO calibration, inter-laboratory variation is ~4% worldwide. INR is a useful measure of warfarin therapy but is unsuitable for assessing the clotting function of liver disease patients, as other bleeding problems may be present concurrently, such as platelet dysfunction. Therefore, prothrombin time and activated partial thromboplastin time (aPTT) should be used for these patients.

Drug interactions

Drug interactions and other disease states can affect the level of anticoagulation with warfarin.[1] These interactions can be divided into pharmacokinetic and pharma-codynamic effects. Pharmacokinetic interactions include enzyme induction, enzyme inhibition and reduced plasma protein binding. Pharmacodynamic interactions include synergism, competitive antagonism (vitamin K) and hereditary resistance to oral anticoagulants. The most serious interactions are those that cause an increase in anticoagulation effect resulting in an increased risk of bleeding. Table 2 summarises the drug interactions and their effects on warfarinisation.

Summary

Warfarin is an effective form of oral anticoagulant and is used therapeutically for various conditions that require long-term anticoagulation. Using the INR to monitor warfarin therapy has allowed greater standardisation between laboratories, and a greater degree of uniformity in clinical practice. Unfortunately, drug interactions are

Table 1: INR ranges based on medical condition (adapted from Lacy CF, Armstrong LL, Goldman MP, Lance LL)[6]

Medical condition	Target INR range
Atrial fibrillation	2.0 – 3.0
Mechanical valve prosthesis (aortic, mitral, leaflet and other types)	2.0 – 3.5
Cardioembolic cerebral ischemic events	2.0 – 3.0
Venous thromboembolism (including deep venous thrombosis)	2.0 – 3.0*
Rheumatic mitral valve disease	2.0 – 3.0
Malignancy-related hypercoagulability	Up to 4

* active treatment of DVT however may necessitate a higher INR of up to 3.5

Table 2: Drug interactions with warfarin (adapted from Blann AD, Fitzmaurice DA, Lip GY)[9]

Enhanced anticoagulation effect: Alcohol, allopurinol, steroids, analgesics (including paracetamol), antiarrhythmics, antidepressants, oral hypoglycaemics, antimalarials, antiplatelet medications, anxiolytics, disulfiram, influenza vaccine, levothyroxine, lipid lowering agents, testosterone, uricosurics.
Reduced anticoagulation effect: Oral contraceptives, retinoids, vitamin K (including dietary supplements).
Variable effect: Antibiotics, cholestyramine, antieplileptics, antifungals, barbiturates, cytotoxics, hormone antagonists, cimetidine.

Note: Although antibiotics are listed as having variable effects on warfarin therapy, generally antibiotics enhance anticoagulation and require more intensive monitoring of the INR while the patient is taking the antibiotic.

very common with warfarin usually resulting in an increased level of anticoagulation and requiring more intensive monitoring of the INR. Nonetheless, warfarin remains the mainstay of outpatient anticoagulation therapy.

Darryl is currently a trainee intern at the Dunedin Medical School and juggles family, friends, study and the military.

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