Warfarin
from rat poison to oral anticoagulant

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Warfarin is now the most widely used long term oral anticoagulant. Due to the narrow therapeutic index and the complexity associated with warfarin therapy, a sound knowledge of the drug is required. This review is aimed at providing some basic concepts on warfarin in use and takes on a UK perspective.

History

The discovery of warfarin was centred around Canada and the US in the early 20th century when sweet clover was planted to feed the cattle. However, as reported in 1921-22 by veterinary pathologist Dr Frank Schofield, improperly cured sweet clover brought a disease to cows characterised by relentless, spontaneous bleeding.[1] In 1940, Campbell and Link isolated the substance dicoumarol that was patented in 1941 for use as a rat poison. However, this was too weak a poison and continued research developed a derivative, patented as warfarin (Wisconsin Alumni Research Foundation + arin to indicate coumarin). Following an attempted suicide by a navy recruit in 1951, clinicians identified warfarin as an anticoagulant and it was clinically introduced in 1952 becoming commercially available in 1954.[1,2,3]

Worldwide the use of warfarin is increasing due to:

a) the increasing number of indications
b) the increasing elderly population [4,5]

Breaking this down to a more localised example in Scotland, since January 1998, the number of warfarin prescriptions dispensed has increased annually from 7 to 11% (Jan 1998 - Dec 2001).[6] Internationally, the increase in use of warfarin and the high risk associated with use of the drug have prompted guideline development. National UK guidelines (also adopted by the BNF) have been issued by the British Society of Haematology in 1998 and SIGN 36 tackling antithrombotic therapy was published in March 1999.[4,5,7]

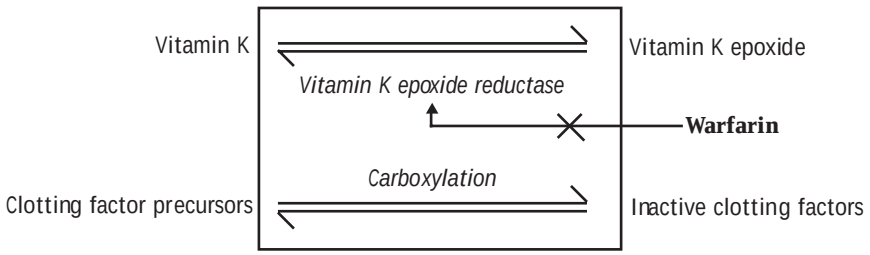
Mechanism of action

Warfarin is a Vitamin K antagonist and consequently inhibits Vitamin K-dependent clotting factors (factors II, VII, IX and X) by inhibiting the enzyme Vitamin K epoxide reductase. This is required for the conversion of clotting factor precursors into inactive clotting factors in the bloodstream. This is summarised in Figure 1.[6]

The inhibition of Vitamin K epoxide reductase by warfarin results in an accumulation of Vitamin K epoxide reducing the effective concentration of Vitamin K and shifting the equation towards the clotting factor precursors. Therefore there is a reduced amount of inactive clotting factors available in the circulation.[9]

Warfarin takes about 50 hours to start exerting its full action since Factor II has the longest half life of 50 hours. Protein C and S, which are naturally occurring anticoagulants, are also Vitamin K dependent and during initiation of treatment there is a possibility of development of a hypercoagulable state where the body's own anticoagulants are British

Figure 1: Schematic representation of the action of warfarin



Oxidation of Vitamin K to Vitamin K epoxide is coupled to the carboxylation of clotting factor precursors to inactive clotting factors. The regeneration of Vitamin K is accomplished by the action of vitamin K epoxide reductase on Vitamin K epoxide. The inhibition of Vitamin K epoxide reductase by warfarin results in reduced concentrations of Vitamin K, and a consequent reduction in the carboxylation of clotting factor precursors to inactive clotting factors.

depressed and warfarin has not yet produced a clinical response. This:

a) is a problem in patients with hereditary or acquired deficiencies of protein C and S and may result in skin necrosis
b) explains why overlap treatment with heparin is required in acute clinical conditions such as Deep Vein Thrombosis (DVT).[6]

Monitoring

There is no linear correlation between the dose of warfarin and its anticoagulant effect. Besides, various factors may cause inter- and intra-individual variation in response to a warfarin dose. It is therefore necessary to monitor the effect of warfarin and this is done through measurement of prothrombin time (PT).[6,9]

The PT is the time taken for a sample of platelets to clot following addition of calcium and tissue thromboplastin, an enzyme from blood platelets that converts prothrombin into thrombin. This is usually about 12 seconds in a non-anticoagulated individual. Thromboplastins are not standardised among manufacturers or between batches. In an attempt to standardise results, the World Health Organisation (WHO) developed a system where thromboplastin is compared to an international reference thromboplastin in order to assign an International Sensitivity Index (ISI). This is used to convert the PT time to the International Normalised Ratio (INR) for a patient and this is the standard of practice.[6,9]

$$INR = \frac{[PT\ patient]^{ISI}}{[PT\ mean\ normal]}$$

Current recommendations for intensity of the most commonly accepted indications are summarised in Table 1. Current guidelines recommend that a target INR be designated for a particular indication rather than a range. An INR within 0.5 units of the target would generally be satisfactory in clinical practice.[4,5] In most settings an INR of 2.5 is the target with higher intensity anticoagulation used in valve replacement and conditions of thrombotic recurrence.

Management of warfarin dosing

Prior to initiation of warfarin therapy, essential baseline investigations include a full blood count including platelets, urea and electrolytes, PT and liver function tests.[6,7] Various protocols are available for the induction of warfarin anticoagulation. The most commonly used method is the Fennerty induction dosing which employs initial doses of 10mg with consequent dosing adjustments depending on the patient's INR.[4,5,7,10] Such a regimen is suitable for the induction of in-patients where rapid anticoagulation is required and where daily INR monitoring is feasible. It provides a predicted maintenance dose on day 4.[10] However, efforts have been made to establish less intense regimens for starting off warfarin which may be especially useful in less acute indications such as anticoagulation due to chronic atrial fibrillation. These may be a safer alternative in elderly patients where a Fennerty regimen may be too severe or where initial daily monitoring is not appropriate. The Tait method employs a 5mg dose from day 1 to day 4 and INR monitoring and dose adjustments on day 5 and day 8. Dose at day 8 predicts the actual maintenance dose.[11] An alternative regimen, established by Oates et al starts the patient at 2mg daily with an INR check on day 8. The dose is adjusted accordingly and the patient returns weekly until the INR is stable (usually defined as the first of two INR results at least 7 days apart which are within target with no dose alteration). This method allows prediction of warfarin dose after two weeks of treatment.[12] Overall, both methods have been shown to result in fewer INRs >4.0.There are few protocols that provide guidance for dosing adjustments during the maintenance phase. The more useful regimens recommend dose adjustments as a percentage change in dose.[13] Dose adjustments should take into consideration individual patient factors such as age, nutritional status, comorbid conditions and any change in drug treatment. Various computer assisted aids have been devised to take variables into consideration to aid in dosing adjustment. A Cochrane review has concluded that computerised prescribing of dosage improved prescribing. This included shorter times to achieve therapeutic control, a reduction in toxic drug levels and incidence of adverse drug reactions and a reduction in the length of hospital stay.[14] Guidance on recall periods during maintenance therapy recommend a maximum recall time of 12 weeks once INR is stable and provided no new factor has arisen (apart from patients with prosthetic valves where a maximum recall of 6 weeks is recommended).[5,7] In a document on anti-coagulation monitoring, the

Medical Association has produced evidence-based criteria for the frequency of monitoring that may be adopted in clinical practice.[15]

This review presents an overview of the development, mechanism of action and clinical use of warfarin. Such a basic knowledge is essential to ensure safe and effective use of the drug. Due to the complexity associated with warfarin therapy, safe use requires an understanding of factors affecting response to warfarin including drug interactions and comorbid states. The latter will be the focus of a second review article.

Table 1: Most common indications for warfarin use. All recommendations are related to warfarin use in adult males and adult non-pregnant females[4,5,8]

Indication	Target INR	Duration
Venous Thromboembolism		
Isolated DVT – calf vein with no risk factors[a] in nonsurgical patients	2.5	3 months
First event PE/proximal vein thrombosis with no risk factors	2.5	6 months
Recurrence of PE OFF warfarin		
a) Two episodes of idiopathic DVT	2.5	Long term
b) Repeated provoked DVT	2.5	6 months or until risk factors resolve
Recurrence of PE ON warfarin	3.5	Long term or until risk factors resolve
Post-op calf vein thrombosis without persistent risk factors	2.5	6 weeks
Post-op calf vein thrombosis with persistent risk factors	2.5	Long term or until risk factors resolve
Recurrence of DVT OFF warfarin		
a) Two episodes of idiopathic DVT	2.5	Long term or until risk factors resolve
b) Repeated provoked DVT	2.5	6 months
Recurrence of DVT ON warfarin	3.5	Long term or until risk factors resolve
Nonvalvular (Non-rheumatic AF)		
Continuous or paroxysmal AF with at least one risk factor to develop thromboembolism[b]	2.5	Long term
AF associated with	2.5	
a) clinical thyrotoxicosis		a) Till controlled
b) intracardiac thrombus		b) As recommended by cardiologist
c) non-cerebral thromboembolism		c) Long term
d) congenital heart disease		d) Long term
Elective cardioversion	2.5	3 weeks before 4 weeks after
AF associated with valvular disease (Rheumatic)		
Rheumatic mitral valve disease ± atrial fibrillation	2.5	Long term
Heart Valve Disease		
Mitral valve prolapse, mitral annular calcification, aortic valve disease + previous systemic embolism or AF	2.5	Long term
Heart Valve Prostheses		
Mechanical heart valves	3.5	Long term
Bioprosthetic heart valves		
After implant surgery	2.5	3 months or as per guidance from cardiac unit
+ associated risk factors[c]	2.5	Long term

a) Cancer, thrombophilia, (antithrombin III deficiency, Protein C and S deficiency, antiphosphopolipid syndrome, chronic infection, inflammatory bowel disease, nephrotic syndrome, pulmonary hypertension

b) Other risk factors: Advancing age (>65 years), history of hypertension, diabetes, heart failure, left ventricular dysfunction, previous ischaemic stroke or TIA, history of thromboembolism. The risk/benefit of warfarin needs to be determined for every individual patient above 75 years of age and needs to be reassessed annually particularly in this age group

c) Risk factors: atrial fibrillation, history of systemic embolism, evidence of left atrial thrombus at surgery, persistent left atrial enlargement, or persistent heart failure

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