

## **Warfarin: Drug Interactions**

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Warfarin is the most widely used anticoagulant drug because of its potency and reliable bioavailability. In terms of usage oral anticoagulants are amongst the most common groups of products used in primary care featuring in the top 50 groups of products, by prescription volume in national statistics (2002 PCA data DOH). Many of the medicines that interact with warfarin appear on the same high volume list in primary care. These include products with the following actions antiplatelets, antibacterials, thyroid hormone and antidepressants, just to name a few. This high volume of prescribing for products with the potential for interaction means that it is important that clinicians are aware of the conditions, diseases and many medicines which can interact with warfarin to potentiate or inhibit its anticoagulant effects.

### **Why are there so many interactions?**

Warfarin only acts in-vivo and the effect is delayed. Its mode of action is to inhibit Vitamin K. Many factors modify its action so regular monitoring and avoiding drug interactions is very important. Warfarin is used orally because it is completely and rapidly absorbed. Food decreases the rate of absorption and major changes in diet especially involving salads, vegetables or increased consumption of alcohol can affect warfarin control. Warfarin is metabolised by the liver via cytochrome P450, and clearance of warfarin is reduced in liver disease. Renal function has little effect on pharmacokinetics or anticoagulant response to warfarin as only small amounts of warfarin are excreted unchanged in urine.

The major adverse effect with warfarin is haemorrhage that occurs at a predisposing abnormality such as ulcer or tumour. However excessive anticoagulation increases risk of bleeding. Close monitoring of the degree of anticoagulation is important. Clinicians are advised to keep treatment periods at a minimum to reduce risks.

### **Uses and Monitoring of Warfarin**

Patients' reactions to warfarin are variable. Fixed induction schemes work for less than 1/3 of patients. Fixed induction was devised to reduce excessive anticoagulation in those patients with increased sensitivity to warfarin and are used to help in dose prediction.

The effect of warfarin is monitored by measuring international normalised ratio (INR) and doses for patients are individualised according to their INR. INR was adopted by the World Health Organisation (WHO) since 1982 and is measured as follows where:

$$\text{INR} = \frac{(\text{Patient's prothrombin time in seconds})^{\text{ISI}}}{\text{Reference prothrombin time in seconds}}$$

(Mean normal prothrombin time in seconds)

(ISI is the international sensitivity index and the WHO reference ISI for Warfarin = 1)

**Standard INR range** for most clinical situations is 2 to 3. In patients who have had recurrent thromboses or have heart prostheses the INR may be 2.5 to 3.5 or even higher.

## **Factors Affecting Anticoagulation**

In addition to dietary changes and excessive alcohol consumption there are other medicines and diseases which affect anticoagulation and which can enhance or inhibit the effects of warfarin. A detailed list of medicines which interact with warfarin is given in Table 1 adapted from BNF 45 Ed. 2003.

### **Enhancing the Anticoagulant Effect**

#### Diseases

- Liver disease interferes with synthesis of clotting factors
- Conditions in which there is a high metabolic rate such as fever and thyrotoxicosis

Classes of Medicines which enhance warfarin effects include products that:

- inhibit drug metabolism.
- inhibit platelet function.
- displace warfarin from binding sites on plasma albumin.
- inhibit reduction of vitamin K and that decrease the availability of vitamin K

### **Inhibiting the Anticoagulant Effect**

#### Conditions and Diseases:

- Pregnancy and other conditions that increase coagulation factors synthesis.
- Oral anticoagulation is lessened in hypothyroidism which is associated with reduced degradation of coagulation factors.

#### Medicines

Some drugs reduce the effectiveness of warfarin - this leads to increased doses being used to achieve the target INR. If the dose of warfarin is not reduced when the interacting drug is discontinued this can result in over-anticoagulation and haemorrhage.

- Vitamin K
- Drugs that induce hepatic P450 enzymes
- Drugs that reduce absorption

**Table 1 Adapted from BNF**

Warfarin Interact with:	Anticoagulation Enhanced	Anticoagulation Reduced	Additional Warnings
Alcohol	■		
Allopurinol	■		
Anabolic Steroids	■		
Analgesics	■		
Anion-Exchange Resins	Cholestyramine can affect anticoagulation both ways		
Anti-Arrhythmics	■		
Antibacterials	■	●	Depends on the Individual Medicine
Antidepressants	Venlafaxine and SSRIs	●	Avoid St Johns Wort
Antidiabetics	Glibenclamide and Tolbutamide (3 isolated reports)		Be Alert for Changes in Anticoagulant and/or Hypoglycaemic effects
Antiepileptics	■	●	Depends on the Individual Medicine
Antifungals	“azoles”	Griseofulvin	
Antimalarials	Proguanil		
Antiplatelet Drugs	■		Avoid Clopidogrel with Warfarin
Antivirals	Ritonavir		
Anxiolytics + Hypnotics	Triclofos and Chloral		
Barbiturates		●	
Bosentan			Manufacturer recommends close monitoring
Corticosteroids	ALTERED		
Cytotoxics	■	●	
Disulfiram	■		
Dopaminergics	Entacapone		
Hormone Antagonists	■	●	Depends on the Individual Medicine
Leukotriene Antagonists	Zafirlukast		
Lipid-regulating agents	■		
Oestrogens + progestogens		Oral contraceptives	
Retinoids		Acitretin	
Sympathomimetics	Methylphenidate		
Testosterone	■		
Thyroid Hormones	■		
Ulcer Healing Drugs	■	●	Depends on the Individual Medicine
Uricosurics	Sulfinpyrazone		
Vitamins		Vitamin K	

Adapted from  
BNF 45 Ed 2003 with additional information from Stockley's Drug Interactions 6 Ed 2003

References:

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