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| **Module** | Management of VKAs (HCP) |
| **Topic** | Factors affecting the INR |
| **Audience** | Healthcare professional |
| **Type** | Content |
| **Version** | 4 |

**1. What should I learn from this topic?**

The aim of this topic is to give you an understanding of how medication, dietary changes, lifestyle and illness can affect action of oral anticoagulants (vitamin K antagonists). The vitamin K antagonist in common use in the UK is warfarin.

By the end of this topic you should be able to:

1. State the factors that may alter the action of warfarin
2. Describe how medicines affect the action warfarin
3. Describe how to manage common drug interactions with warfarin
4. State how changes in diet may affect the action of warfarin
5. Describe how alcohol may affect anticoagulation

**2. Check your understanding**

Before you start reading this topic check how much you already know by taking a short quiz. You will have an opportunity to take the quiz again at the end of the module, where we will reveal the correct answers.

a) Which of the factors listed below are likely to alter the effect of warfarin? (please select any that apply)

1. **Other medication**
2. **Alcohol**
3. Taking warfarin on a full stomach
4. **Changes in diet**
5. **Getting a dose of ‘flu**
6. Taking warfarin with a glass of milk

**b)** The most common way that drugs affect the action of warfarin is by reducing its excretion by the kidneys.

True **/ False**

c)On introducing a drug that inhibits the cytochrome P450 system to a patient taking warfarin, the following takes place:

* 1. **INR increases, necessitating a warfarin dose reduction**
  2. INR increases, necessitating a warfarin dose increase
  3. INR drops, necessitating a warfarin dose reduction
  4. INR drops, necessitating a warfarin dose increase

d) Rifampicin is an enzyme inducer. When taken with warfarin, this means that warfarin is:

* 1. **metabolised more rapidly, resulting in a lower INR**
  2. metabolised more rapidly, resulting in a higher INR
  3. metabolised more slowly, resulting in a lower INR
  4. metabolised more slowly, resulting in a higher INR

e). On the introduction of an interacting drug to be taken for 1 week or more, it is important to check the INR on a weekly basis

**True** / False

f). It is reasonable to halve the dose of warfarin if a broad-spectrum antibiotic like co-amoxiclav is introduced.

True **/ False**

g). The use of alternative medicines such as glucosamine and cod-liver oil, together with warfarin is safe

True / **False**

h) Those taking warfarin should be advised to avoid food containing vitamin K

True / **False**

i) Binge drinking reduces the INR

True / **False**

**3. How do other drugs interact with warfarin?**

Many drugs can interact with warfarin. They can enhance or reduce the effect of warfarin, which can lead to an increased risk of bleeding or thrombosis.

These drug-drug interactions can either be **pharmacokinetic** or **pharmacodynamic**. With a pharmacokinetic interaction, the second drug will affect the absorption, distribution, metabolism, or excretion of warfarin. In a pharmacodynamic interaction, the second drug will enhance or antagonise the effect of warfarin.

**POINTS TO PONDER?**

Have you come across someone who took another drug that interacted with warfarin? What was the other drug? How did you manage it?

**3.1 Pharmacokinetic interactions with warfarin**

Metabolism is the process by which drugs are converted into a form that can be excreted **(metabolites**). The rate of metabolism determines both the duration and intensity of a drug's action.

Like many other drugs, warfarin is metabolised in the liver. A family of enzymes in the liver known as cytochrome P-450 is responsible for breaking warfarin down into metabolites, which are then excreted through the bile or the kidney.

Drug-drug interactions can occur when the second drug reduces **(inhibits)** or increases **(induces)** the effect of the cytochrome P-450 enzyme that is breaking down warfarin. A drug that induces cytochrome P450 enzyme will enhance the metabolism of warfarin, which may lead to lowered concentrations of warfarin. Conversely, if a drug inhibits cytochrome P450, this may lead to excessive levels of warfarin. In most cases, changing the dose of warfarin will compensate for the action of the second medication.

Although not an exhaustive list, here are examples of medicines that can affect the metabolism of warfarin.

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| **Medicines that can increase levels of warfarin (increase INR)** | Amiodarone  Fluconazole  Metronidazole  Allopurinol  Ciprofloxacin  Rosuvastatin  Ciprofloxacin  Clarithromycin  Omeprazole  High dose corticosteroids (e.g. prednisolone) |
| **Medicines that can decrease levels of warfarin (decrease INR)** | Carbamazepine  Phenytoin  Rifampicin  Pioglitazone  Griseofulvin |

**Medicines that can affect the metabolism of warfarin**

**3.2 Pharmacodynamic interactions with warfarin**

Although pharmacodynamic interactions with warfarin are not as numerous as pharmacokinetic interactions, they are important. Examples of these interactions are given below. Note that these drugs may increase the risk of bleeding without necessarily increasing the INR.

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| **Antiplatelet agents including aspirin** | Pain-killing doses (300 – 600mg) of aspirin increase the risk of bleeding and can damage the stomach. If a pain-killer is needed, paracetamol is a safer option, but it is essential that the maximum dose of 4g in 24 hours is not exceeded  Low dose aspirin (75 – 150 mg) is safer, and in some circumstances is prescribed with warfarin. |
| **Non-steroidal anti-inflammatory drugs (NSAIDs)** | For example, ibuprofen (Nurofen (T)), diclofenac, naproxen  As aspirin. Should be avoided if possible. |
| **Some antidepressant drugs** | For example; sertraline, fluoxetine, citalopram, paroxetine |
| **Levothyroxine** | Increases catabolism of clotting factors |

**Examples of pharmacodynamic interactions that may increase the risk of bleeding with warfarin**

Many **herbal/natural products** also have antiplatelet effects, and although their additive affect is less predictable, evidence for their potential to increase the risk of bleeding is growing. These are discussed further in section 7.

**3.3 Top tips for managing warfarin drug interactions**

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| * The use of interacting drug is difficult to avoid and therefore patients should be encouraged to report every drug change/addition to the anticoagulant practitioner. This message should be reinforced at frequent intervals |
| * Providing details of these drug changes will enable to practitioner to decide whether the INR needs to be checked sooner rather than later. |
| * The British Committee for Standards in Haematology (BCSH) guidelines state:   Drug change of < 5/7 duration – either: no change, minor dose alteration or omit/load one dose  Drug change of > 5/7 duration -> check INR 1/52 after starting interacting drug, a  minor dose alteration or omit/load one dose |
| * Treat **any** drug as having the potential to interact with warfarin. Until you are familiar with how a drug interacts with warfarin and how significant the interaction is, it is best to manage cautiously. |

**3.4 Drug interactions – the ‘usual suspects’**

Although all drug additions should be viewed with caution, in practice there are some ‘usual suspects’ … i.e. drug interactions that are more frequently encountered. These are summarised below.

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| **Interacting drug** | **Action** | **Suggested management** |
| **Amiodarone** | Increases INR in most patients due to amiodarone’s effect of inhibition of liver enzymes. Onset is slow, but usually develops within 2 weeks. | Monitor patient on a weekly basis for the first 4 weeks of treatment.  Interaction may persist for many weeks after the amiodarone has been withdrawn; so weekly blood tests are necessary on withdrawal also. |
| **Antibiotics** | Highly unpredictable interaction, but experience in clinic has found that broad-spectrum antibiotics frequently cause an increase in INR.  The hypothesis for this interaction is that some microbial flora are responsible for the cleaving and making available for absorption of vitamin K from diet. Broad-spectrum antibiotics destroy the microbial flora, thereby reducing the amount of vitamin K available to be absorbed, thereby increasing the INR. Occasionally, broad-spectrum antibiotics decrease the INR, but the mechanism of this interaction is unclear. | In some circumstances, a slight decrease in warfarin dose (e.g. 0.5 mg / 1mg) for the duration of course may be advisable, and this may be sufficient to minimise the predicted INR rise. The decrease can be undertaken as a pre-emptive strike if the patient informs you before they start the course, or after the INR test, if the antibiotics are for one week or more. |
| **Rifampicin** | This can be a problematic interaction as rifampicin is a potent enzyme inducer. The onset of the interaction is slow, usually developing within 2-6 weeks. | Weekly INR checks are necessary together with dose titrations, until a new stable dose is established. On stopping rifampicin, weekly INR checks will again be necessary.  For VTE patients, it may be necessary to ‘bridge’ with the use of a low molecular weight heparin. |
| **Statins** | Effects are variable. Pravastatin is unlikely to effect action, as it has no effect on liver enzyme activity. Atorvastatin can reduce effect by induction of liver enzymes, although the effect is slight and usually transient. Other statins may enhance the INR – e.g. simvastatin and rosuvastatin. | Monitor INR more closely until the effect of the statin is clear. |
| **Cranberry juice** | Enhances anticoagulant effect of warfarin by enzyme inhibition. | The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK has advised against the use of cranberry juice whilst taking warfarin. If the patient wishes to use, INR checks are required on a weekly basis to assess its effects. |

**Management of common drug interactions with warfarin**

**3.5 Where can I find more information about warfarin drug interactions?**

The following are valuable sources of information:

1. [**Warfarin Interactions**](http://www.anticoagulationeurope.org/files/files/Some%20of%20the%20most%20common%20interactions%20with%20warfarin%20.pdf)  (*www.anticoagulationeurope.org/files/files/Some%20of%20the%20most%20common%20interactions%20with%20warfarin%20.pdf)*

- an information sheet produced by Anticoagulation Europe, a UK-based patient advocacy group

2. The [**British National Formulary**](http://www.bnf.org/) (BNF) *(www.bnf.org)*

The BNF is a joint biannual publication of the British Medical Association and the Royal Pharmaceutical Society. It is designed as a rapid reference to guide the selection, prescribing, dispensing and administration of medicines.

3. The Summary of Product Characteristics (SPC) for the individual medicine. An SPC tells healthcare professionals how to prescribe and use a medicine correctly and includes a comprehensive list of its drug interactions. The SPC for most products can be accessed [**here**](http://www.medicines.org.uk/emc/). *(http://www.medicines.org.uk/emc/)*

**3.6 How do herbal and natural remedies interact with warfarin?**

As discussed earlier, natural and herbal remedies may interact with warfarin. Common examples are shown below. Please note that this is not a complete list and all natural remedies should be treated with caution.

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| Chondroitin | Chondroitin also has anticoagulant activity and should be avoided |
| Cranberry juice | Likely to enhance the effect of warfarin. Avoid use. |
| Devil’s Claw | May enhance the effect of warfarin. |
| Fenugreek | May increase the risk of bleeding |
| Feverfew | May increase the risk of bleeding |
| Fish oils (e.g. cod liver oil) | May increase the risk of bleeding |
| Garlic | May increase the risk of bleeding. Do not take garlic supplements. However, regularly eating foods containing small amounts of garlic should not be a problem. |
| Ginger | Large amounts may increase the risk of bleeding |
| Gingko Biloba | Increased risk of bleeding |
| Ginseng | Increased risk of bleeding |
| Glucosamine | Likely to enhance the effects of warfarin. Avoid use |
| Grapefruit juice | May enhance the effect of warfarin. Avoid or use cautiously. Note that the fruit itself (i.e. not the squeezed juice) is likely to be safe in small quantities. |
| Multivitamin supplements | Use cautiously. May contain ingredients that affect warfarin metabolism e.g. Ginseng |
| St John’s Wort | Reduces the effect of warfarin. Avoid use |

**Natural remedies that can interact with warfarin**

**4. How do changes in diet affect warfarin?**

*(Image 118\_MP900402672.JPG)*

Warfarin acts by preventing the formation of **vitamin K-**dependent clotting factors. Vitamin K is not stored in the body but is supplied from food. Therefore, if the amount of dietary vitamin K increases, the effect of warfarin can be significantly reduced.

Those taking warfarin should avoid natural remedies that contain vitamin K, including health foods and food supplements. Additionally, alfalfa contains large amounts of vitamin K and Co-Enzyme Q10 is very similar to vitamin K. Both remedies should be avoided.

Examples of foods that contain significant quantities of vitamin K are listed below:

* **Turnip greens**
* **Beetroot**
* **Broccoli**
* **Cabbage**
* **Lettuce**
* **Spinach**
* **Avocado**
* **Green beans**
* **Liver**
* **Soya bean products**
* **Peas**

Vitamin K-containing foods form part of a healthy diet, and patients should not be advised to omit these completely. Instead, patients should be counseled to keep the amount of vitamin K-containing foods in their diet consistent, and to inform their anticoagulant practitioner if they have changed their diet since the last INR test.

**4.1 Where can I find out the amount of vitamin K in different foods?**

The amount of vitamin K contained in foodstuffs can be found here (http://www.ptinr.com/cafe-ptinr/vitamin-k-finder)*)* On this page you will also find a diary that may help patients track their intake of vitamin K containing foods.

**5. How does alcohol affect warfarin?**

Alcohol has complex pharmacokinetics. **Chronic use** induces liver enzymes, whilst **acute use** inhibits these enzymes. Therefore, binge drinking dramatically increases INR and puts the patient at a greater risk of bleeding. Conversely, chronic heavy alcohol usage may result in increased warfarin requirements.

This is another area where **patient counseling is essential**. Those taking warfarin should be advised on **drinking limits** – no more than three units of alcohol a day for a man, or two units a day for a woman. One unit is roughly equivalent to half a pint of beer or lager or a single measure (25ml) of a spirit such as vodka. A small glass (125ml) of wine is around 1.5 units (Figure A). Patients should be advised against big variations in the amount they drink from day to day and particularly against binge drinking. Patients should be also be encouraged to let their anticoagulant practitioner know if they have changed your alcohol intake since their last blood INR test.

*Placeholder for image of alcohol units*

**POINT TO PONDER**

For the second time in a month, a patient confesses to binge drinking, which has elevated his INR. How would you counsel him?

**6. How do changes in health affect the INR?**

Changes in health can affect the way warfarin works, which may necessitate more frequent INR tests. Examples include the following:

**Enhancing the effect of warfarin:**

* Liver impairment
* Exacerbation of CCF
* Renal impairment
* Infective episodes (e.g. cold, ‘flu)
* Steatorrhoea
* Hyperthyroidism

**Reducing the effect of warfarin**

* Acute diarrhoea
* Vomiting

**7. Other factors affecting the response to warfarin – age and concordance**

Increasing age affects a person’s ability to metabolise warfarin. Liver and renal function reduces as we age and, consequently, the dose requirement for warfarin reduces. It has been suggested that for each decade, a person is on warfarin, their dose reduces by 1mg daily

Not taking medications as prescribed is an acknowledged prevalent issue. Missing a dose of warfarin will result in a small change in INR, several days after missing it.

**POINT TO PONDER**

You suspect that one of your patients has not been taking her warfarin as prescribed. How would you question her about this?

**DEMONSTRATE YOUR UNDERSTANDING**

Finally, please try to answer the questions at the start of this topic again. Did you get a higher score?