

INR Testing

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Sweet Clover
Melilotus alba

Using INR when
Initiating Warfarin therapy

Frequency of INR testing

Why does INR Change?

In 1933, a farmer in Wisconsin reported spoiled hay and dying cattle. The sweet clover to be used as a hay crop had been improperly cured, and as a result had become infected with mould. The mould was able to metabolise the coumarin in the hay to dicoumarol, a powerful anticoagulant. Since the 1950s Warfarin has been used throughout the world as a rat poison and an anticoagulant in humans. (Last, 2002)

During Warfarin therapy it is important to use the INR to guide you in providing the balance between minimising the risks of bleeding while providing the benefits of anticoagulation.

What is INR?

The basis of the test used to monitor Warfarin therapy is the one-stage prothrombin time (PT). The International Normalised Ratio (INR) has become the standard laboratory value for monitoring and adjusting Warfarin therapy and therapeutic ranges have been established in terms of the INR. The INR was developed as a means of standardising PT values. Using this system, each thromboplastin is standardised against a WHO standard, and as is assigned an International Sensitivity Index (ISI) value. This enables Warfarin therapy to be managed more effectively as patients travel, relocate, or obtain care from more than one health provider.

$$\text{INR} = \left(\frac{\text{Patient PT}}{\text{Mean normal PT}} \right)^{\text{ISI}}$$

Using INR when Initiating Warfarin Therapy

- Warfarin is not fully effective against clot formation for up to 5 days because the circulating clotting factors must be cleared first (Hirsh, 2003)
- For this reason the first INR test is usually on day 3 of therapy (Jaffer, 2003)
- For most patients the INR range will be 2.0 - 3.0, with a target of 2.5 (Ginsberg, 2001)
- Some patients, for example those with mechanical heart valves may require higher target INRs. Advice from a haematologist may be required.

Warfarin should not be used as the first line of treatment in the presence of active clot formation. Heparin must be administered with Warfarin for at least 5 days and until the INR has been therapeutic for two days - Dr Ian Morison (Haematologist)

Frequency of INR testing (from day 3 of therapy)

- The INR is considered stable when two or more consecutive tests are within the target range (usually 2 - 3)
- Fluctuations of the INR value within the target range are not considered unstable, and adjustment of the dose is usually not required (BC Health Services, 2004)

<i>Initially:</i> every 2 days	Until stable for 2 consecutive tests
<i>Once stable:</i> every 3 - 5 days	Until stable for 2 consecutive tests
<i>Once stable:</i> weekly	Until stable for 2-3 consecutive tests
<i>Maintenance:</i> practitioners should aim for 4 - 6 weekly testing in patients with well controlled INRs, however a minority of patients may require more frequent testing	

Adapted from Reference: Horton, 1999

Why do some patients INR values fluctuate?

Fluctuations in the INR value may be due to a number of reasons:

1. Non adherence to dosage regimen
2. Drug interactions (pharmaceutical or herbal)
3. Major changes in diet
4. Systemic or concurrent disease
5. Unknown causes

1. Non adherence to dosage regime

An erratic INR may reflect non-adherence to the drug regimen, most often this would be due to a misunderstanding with dosage requirements. A missed dose of Warfarin is generally reflected in the INR result, 2 to 5 days after the dose was missed (Jaffer, 2003), although a dose response relationship may be seen within 16 hours (National Guideline Clearinghouse, 2004).

2. Drug interactions

When prescribing new medication to a patient on Warfarin, or adding Warfarin to a current regimen, it is essential that possible drug

Drug interactions with Warfarin should be considered when almost any drug or herbal medicine is added or removed from the patient's regimen of treatment (Hirsh, 2003)

interactions are considered. In particular, co-trimoxazole should be avoided when possible. NSAIDs, sulphamethoxazole, erythromycin family, ciprofloxacin family, phenytoin and ethanol also have well reported interactions with Warfarin. Sources of information on Warfarin drug interactions can be found in resources such as your practice management system, MIMS, and BNF.

Drugs that often cause the most disturbances are those used intermittently, and as a result INR requires closer monitoring. Medication used in chronic conditions usually only requires closer monitoring of the INR when the drug is initiated or discontinued (Horton, 1999).

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The use of herbal medicines is gaining increasing popularity, but in most cases the decision to use herbal medicines is not discussed with the GP (Smith, 2004), and the number of studies performed on the interactions with Warfarin is rather limited. Therefore, it would be prudent to assume any herbal medication may have the potential to alter the INR.

Due to the potential interaction with Warfarin, always ask patients if they are taking any herbal medicines

Common herbal medicines thought to interact with Warfarin (Smith, 2004)

Name	Potential effect
Garlic	Increased risk of bleeding
Ginseng	Increased risk of bleeding
Ginkgo biloba	Increased risk of bleeding
Feverfew	Increased risk of bleeding
Ginger	Increased risk of bleeding
St John's wort	Increased risk of clotting

3. Diet

Patients on Warfarin therapy are usually advised to consume a reasonably consistent proportion of vitamin K rich foods. This is probably most relevant in patients who have markedly reduced food intake because of illness, hospitalisation, postoperatively, travel and fad diets, (Campbell, 2001). A recent study suggests that the role of dietary vitamin K may have been overstated, with the exception of natto (Japanese fermented soybean) which causes a marked and prolonged inhibition of Warfarin (Schurgers, 2004).

4. Systemic or concurrent disease

- *Congestive heart failure*: may cause hepatic congestion of blood flow and inhibit Warfarin metabolism. This may be particularly troublesome during exacerbations of heart failure.
- *Hypothyroidism*: decreased catabolism of vitamin K clotting factors may decrease INR values.
- *Hyperthyroidism*: conversely, hyperthyroidism may increase catabolism of vitamin K clotting factors and may increase INR values.
- *Liver failure*: may cause elevation of INR due to reduced production of clotting factors
- *Other illnesses*: other intermittent conditions such as fever, vomiting and diarrhoea may affect the INR; ill patients may also reduce their usual dietary intake.

5. Unknown causes

In many cases, no explanation may be found for unstable INR values. It may be worthwhile discussing aspects of the dosing regimen. Changes in the INR may also be the result of occult causes, which may include undisclosed drug use, lifestyle and medical causes.

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