QUESTIONS FOR CHRONIC WARFARIN PATIENTS EXPERIENCING FLUCTUATING INR’S

There are many reasons for variance in INR’s in patients on warfarin. Even a patient who has been stabilized on warfarin for some time may experience unexpected fluctuations. These fluctuations may be driven by both pharmacokinetic (eg drug interactions) and/or pharmacodynamic (eg vitamin K intake) factors. This checklist is designed to enable prescribers to obtain a relevant history from the patient, which will help them to determine the cause for the change in INR. This in turn will help to make rational decisions regarding any dose changes in warfarin, or suggestions to the patient, which may help eliminate these fluctuations. A list of suggested questions to ask the patient is given below, followed by the rationale behind asking the questions.

1. **REGULARITY OF TESTING**
   - **Do you have blood tests for warfarin every 2-4 weeks?**
     If you are seeing a new patient it should be established that they have indeed had regular INR’s performed. There have been anecdotes of patients started on warfarin who have gone 6 months or more without having an INR done.

2. **COMPLIANCE**
   - **Do you manage to take the warfarin every night or do you sometimes forget?**
     If the INR is unexpectedly low, always query the patient re compliance.
   - **If you forget, do you take an extra dose to make up for it?**
     It has been known for patients to take extra doses to make up for missed doses, especially leading up to a doctor’s appointment. If a patient misses a dose and remembers within 12 hours of the missed dose it is OK to take an extra dose at this point. If they don’t remember until greater than 12 hours later then it is best to not make up for the missed dose.

3. **PRESCRIBING ERROR OR CHANGE OF BRANDS**
   - **Have you recently changed brands of warfarin?**
     Although warfarin is rapidly and completely absorbed there are some case reports indicating that changing brands may affect the INR. Patients should be counselled to use the same brand.
   - **Is the colour of the tablet the same as it was several weeks ago?**
     This simple question can help rule out the possibility of a dispensing error, or check to see if the brand has changed. The different strengths of warfarin are generally distinctly colored.
4. **DRUG INTERACTIONS**

   - **Have you recently, in the last 3-4 weeks, started or ceased any drug therapy or medications, including antibiotics for an infection?** Antibiotics, especially macrolides (erythromycin, roxithromycin and azithromycin), imidazoles (fluconazole, ketoconazole, metronidazole, miconazole (including oral gels)) and ciprofloxacin may increase the INR. This is generally seen within a week of starting antibiotic therapy and the extent of the interaction is often unpredictable. Rifampicin is the only antibiotic that can lower INR. It is prudent to increase the monitoring of INR more intensely for several weeks when stopping or starting any drug therapy.

   - **Do you take any non-prescription drugs, vitamin tablets, herbal preparations or mouth gels/paints?** Patients may not identify non-prescription drugs or herbal products as medications. A product such as miconazole mouth gel can cause a huge rise in the INR. Multivitamin tablets with significant doses of vitamin K may lead to warfarin resistance and a low INR.

   - **Are there any drugs that you take only when you need them, such as painkillers or headache tablets?** Patients may not identify “prn” medications as such. This includes NSAID’s and paracetamol containing products. Increased intakes of paracetamol (>5g/week) have been associated with increased INR’s, but it should be noted that paracetamol is still the recommended analgesic if pain relief is required.

5. **DIET**

   - **Have there been any changes in your eating habits recently?** Warfarin is a vitamin K antagonist and exerts its influence by inhibiting the vitamin K dependent clotting factors (II, VII, IX and X). The INR reflects the balance between the vitamin K status and the warfarin dose. Patients eating a diet high or low in vitamin K (eg broccoli, spinach, lettuce, beans or brussel sprouts) may respectively exhibit resistance (low INR’s) or sensitivity (high INR’s) to warfarin. Patients should be encouraged to be consistent with their diet.

   - **Have you “gone off” your food lately?** Elderly patients often partake in only marginally satisfactory diets, hence marginal vitamin K status. This may be reflected by a low serum albumin (<32g/l). These patients may be very sensitive to the effects of warfarin and experience fluctuating INR’s depending on their dietary habits and hence their vitamin K status. Even something like a flare-up in arthritis may restrict patients mobility and discourage them from preparing a normal meal, therefore upsetting the warfarin/vitamin K balance.
• How many alcoholic drinks do you have each day? Has this increased or decreased in the last few weeks?
  1-2 glasses of alcohol per day may increase warfarin metabolism, but chronic alcoholism may lead to a vitamin K deficient diet or poor compliance.

6. CO-MORBIDITIES

• Have you had any new medical illnesses or worsening of current, known medical illnesses in the last month?
  Patients experiencing exacerbations in severe airways disease or severe CCF may experience increases in INR, possibly due to decreased hepatic oxygenation resulting in decreased elimination. Many patients will also experience a decrease in appetite during acute illnesses, or during exacerbations in known illnesses, which may upset the balance between warfarin and vitamin K and lead to an increased INR.

• Have you experienced any diarrheal illnesses in the last week?
  Warfarin is completely and rapidly absorbed and unaffected by diarrheal illnesses. It is likely though that decreased absorption of vitamin K increases the sensitivity to warfarin, upsetting the warfarin-vitamin K balance, resulting in a rising INR.

These questions concentrate on a time frame of the prior 3-4 weeks. The reasons for this are:
  a) It is assumed that most patients will have had an INR done in the previous month, which was relatively normal
  b) The time frame for both pharmacokinetic and pharmacodynamic interactions is generally a maximum of several weeks.

7. REFERENCE

Questions and answers prepared by Mr. Greg Roberts (Pharmacist).