

The complexity of treatment with warfarin

Antonella Tonna BPharm (Hons), MSc, MRPharmS¹

Ivan Tonna MD, MRCP, MSc²

¹ School of Pharmacy, The Robert Gordon University, Schoolhill, Aberdeen, UK

Email: prs.tonna@rgu.ac.uk

² Specialist Registrar, Raigmore Hospital, Inverness, UK

Email: ivantonna@doctors.net.uk

Key words: warfarin, metabolism, interactions, contraindications, side effects

Maintaining a patient within a therapeutic international normalized ratio (INR) is the main aim of treatment with warfarin. Anticoagulation above or below the therapeutic window may result in bleeding or thrombosis respectively. This is made more complex by the numerous factors that may affect warfarin management including other drugs, diet and disease. This review aims to highlight factors that may affect therapy with oral anticoagulants (Figure 1). A sound knowledge of such factors ensures safe administration of warfarin.

Warfarin and other medications

There may be two forms of interactions between warfarin and other drugs:¹

a) Pharmacokinetic interactions

which include:

- Alteration in absorption: This may involve an alteration in absorption of either vitamin K or warfarin. It may include alteration of gut flora causing reduced availability of vitamin K (eg some broad spectrum antibiotics)²,

or binding with warfarin resulting in reduced absorption (eg cholestyramine or colestipol).^{2,3} In the latter case, separating the two drugs by 4-6 hours may help overcome this interaction.³

- Interference with warfarin metabolism: Drugs may inhibit or induce cytochrome (CYP) enzymes involved in the metabolism of warfarin and may therefore alter the plasma concentrations of warfarin. Warfarin is a racemic mixture

with the (S) form being five times more potent than the (R) form.⁴ Hepatic metabolism involves separate pathways, and drugs may exhibit stereoselectivity by inhibiting one form but not the other. The (S) form is metabolized by CYP2C9 and the R-isomer metabolised by CYP1A2, CYP2C19 and CYP3A4.⁵ Drugs which interfere with CYP2C9 have a more clinically significant effect on anticoagulation. Examples of inducers include rifampicin and barbiturates while metronidazole is a potent enzyme inhibitor.^{2,3}

- Displacement from protein binding sites: The clinical significance of reductions in plasma protein binding by interacting drugs has been debated. Protein-bound warfarin is in equilibrium with free warfarin such that around 99% is bound; displacement of warfarin from serum proteins will result in an increased amount of free drug, making it available to move to the intracellular sites of action and to be excreted. The effect is usually described as transitory and said only rarely to require warfarin dosage adjustment because the increased free drug is metabolised or excreted and a new equilibrium established.^{5,6}

b) Pharmacodynamic interactions:

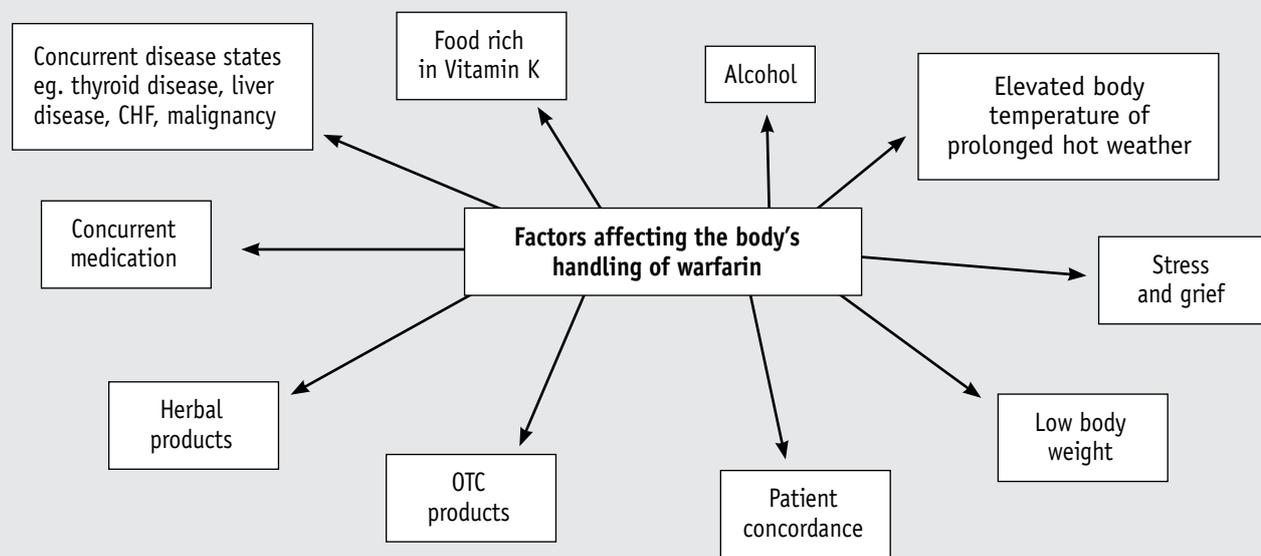
Some drugs affect platelet function by reducing platelet aggregation. Thus, even though these drugs do not affect the INR, they may be associated with an increased risk of bleeding. Examples include aspirin, dipyridamole, clopidogrel and ticlopidine.^{2,3}

Warfarin and alternative therapies

Several alternative therapies may have the potential to interact with warfarin. However, due to a lack of available information, the clinical significance of potential interactions is often unknown since most information is related to *in vitro* data, case reports and theoretical interactions. Overall, patients on warfarin should be advised not to self-treat with such therapies. Often, patients do not mention herbal medications to their health care professional believing that these are safe and will not interact with conventional

Figure 1

Summary of some factors that may affect the body's handling of warfarin



medication.^{7,8} One UK study found that as many as 92% of patients who were taking herbal medications with warfarin did not inform a health care professional.⁷

Herbal medications may interact with warfarin as follows:^{1,9-12}

- They may contain substances that have coumarin, salicylate or antiplatelet properties. Though there have been no documented case reports, there is a theoretical risk for potentiation of warfarin activity (e.g., anise, chamomile, red clover)
- They may interfere with haemostasis and platelet aggregation (e.g., feverfew, garlic, ginger)
- They may be structurally similar to vitamin K or contain large amounts of vitamin K and consequently have a procoagulant effect (e.g., Coenzyme Q₁₀, Green tea)
- They may interfere with metabolism of warfarin through inhibition or induction of cytochrome system (e.g., Ginseng and St John's wort both inhibit the cytochrome P450 system)

Dietary supplementation may affect warfarin levels as follows:^{10,13,14}

- Minerals are suspected to bind to warfarin and therefore inhibit its absorption. Administration of warfarin

should be separated from intake of these minerals by a period of 2 hours.

- With the exception of vitamin K, vitamins are unlikely to interact unless taken at doses larger than the recommended daily dose.
- Vitamin K directly antagonises the effects of warfarin. Therefore patients should be advised to take a vitamin K free preparation or be consistent in the use of multivitamins containing vitamin K.

Table 1 summarises some practice points to aid in the safe management of patients on oral anticoagulation who are also on alternative therapies. Producing an exhaustive reference list of interactions with warfarin is beyond the scope of this review article. The reader is provided with some recommended references at the end.

Warfarin and food

Foods may affect warfarin levels particularly if they contain a high vitamin K content.¹⁵ Table 2 provides a list of such foods. It is important to keep in mind that enteral feeds may contain a large amount of vitamin K. Patients on weight reduction diets tend to have diets based on leafy vegetables which may contain large amounts of vitamin K. In such cases, patients should be advised to keep constant intakes of these foods.^{14,15} Alcohol may also

affect warfarin levels.¹ Chronic alcoholics may experience a diminished effect from warfarin due to stimulation of hepatic metabolism by alcohol. In the case of 'binge' drinking, there may be an increase in effect of warfarin due to the inability of the liver to metabolise and synthesise clotting factors. Alcohol is considered safe in people with normal liver function provided there is an intake no greater than 2 units daily.¹

Other factors affecting warfarin metabolism

The following is a summary of possible factors affecting warfarin metabolism:

- Thyroid disease:** Hypothyroidism results in a reduced metabolic rate with clotting factors remaining in the circulation for longer and result in higher requirements for warfarin. When thyroid replacement hormones are administered, the metabolic rate will increase as it returns to normal and clotting factors are metabolised more rapidly. The requirements for warfarin thus decrease. Similarly, when doses of thyroxine are increased, warfarin requirements fall. It is therefore necessary to check the INR after 4-7 days, then weekly until this is stable. The reverse applies if doses of thyroxine are reduced. Hyperthyroidism results in an accelerated metabolic rate with clotting factors being cleared at

Table 1

Ensuring safe use of alternative medications

- 1.1 Herbal medications also have the potential to interact with warfarin
- 1.2 Always assume an interaction occurs unless there is evidence to the contrary
- 1.3 When there is a potential for interaction:
 - 1.3.1 Patient should be advised to stop the drug before starting warfarin
 - 1.3.2 If patients insist on taking these medicines, more frequent INR monitoring and closer observation for signs and symptoms of bleeding is recommended
 - 1.3.3 If a patient self-administers a remedy without advice, it is prudent to ask the patient to stop and recheck INR within 4-7 days and then at regular intervals until stable
- 1.4 When a documented report of interaction exists, consider the combination as contraindicated due to a potential risk of thrombotic complications
- 1.5 Ask patients about the use of alternative therapies since they often will not inform you
- 1.6 Information is often obtained by patients through alternative sources as opposed to health care professionals
- 1.7 Patients are less likely to report adverse events from herbal interactions
- 1.8 Herbal products may have several common and scientific names

Table 2

Foods that may affect warfarin levels

Asparagus	Endive (chicory)	Scallion
Avocado	Green beans	Soya bean products
Beef liver	Green tea	Spinach
Broccoli	Kale	Swiss chard
Brussel sprouts	Lettuce (including red)	Tonic water (quinine)
Cabbage (green)	Liver	Turnip greens
Collards (white cabbage)	Mint	Water cress
Coriander	Parsley	

a faster rate. Therefore lower doses of warfarin are required. If antithyroid drugs are administered (eg propylthiouracil or carbimazole), the metabolic rate will slow down and therefore the requirements for warfarin will increase since clotting factors will remain in the blood stream for a longer time.^{1,3,13,16}

b) Elevated body temperature (pyrexia or hyperthermia): This results in an accelerated metabolic rate with clotting factors being cleared at a faster rate. Therefore lower doses of warfarin are required.^{1,13}

c) Liver disease: This may result in various effects on coagulation, including vitamin K deficiency due to intra- or extra-hepatic cholestasis, reduced synthesis of coagulation factors due to severe hepatocellular damage and functional abnormalities of platelets and fibrinogen found in patients with liver failure. Consequently, the effects on INR are unpredictable and closer INR monitoring is required.^{1,13}

d) Stress and grief: These have an unpredictable response. Patients may require closer monitoring in such situations.^{1,13}

e) Patient concordance: Possible lack of patient understanding of the risks associated with anticoagulation therapy may result in patient nonconcordance resulting in a variable and unpredictable response.^{1,13}

f) Low body weight: Increased sensitivity to warfarin may require reduced dosing.¹³

g) Malignancy: Treatment with cytotoxic agents and metastases to the liver may lead to an increased sensitivity to warfarin.¹³

h) Congestive heart failure: Hepatic congestion due to heart failure may lead to an increased sensitivity to warfarin.^{1,13}

Other risk factors that may result in a variable anticoagulation response are:¹⁷⁻¹⁹

- Multiple warfarin dosage changes (>4 changes within 6 months)*
- Inappropriate warfarin dosage change
- Addition of a new drug potential for interaction (short course antibiotics have been most often implicated)*
- Administration of multiple medications (>4)
- Risk factors for gastrointestinal (GI) tract bleeding include a past history of gastrointestinal bleeding, concomitant use of conventional NSAIDs
- Comorbid conditions associated with higher risk for intracerebral bleeding – including uncontrolled hypertension (persistently > 160/90), cerebrovascular disease, head trauma, concomitant use of conventional NSAIDs
- Malnutrition and malabsorption
- Other decompensating systemic illness (especially infection, disseminated intravascular coagulation).

Evidence is conflicting with respect to patient age with some studies indicating an increased risk and others finding no association between age and oral anticoagulants. The risk-benefit should however be assessed in patients aged over 75.¹⁸ Patients on high intensity anticoagulation appear to have a higher risk of being out-of-control since a higher target INR is usually aimed for.^{17,18}

Various studies involving retrospective analysis of patient data have concluded that mortality is lowest when the INR is within

* Most common risk factors implicated

the range of 2.2.-2.3. An INR >6.0 indicates a risk of major haemorrhage in the next 14 days despite no current signs of bleeding.²⁰

Adverse effects

The main adverse effects of warfarin are:^{1,16,21}

- Increased risk of bleeding which is not necessarily accompanied by a high INR and which is related to the inherent property of warfarin as an anticoagulant. Patients need to be informed about this risk and what action to take in case of bleeding.
- Skin necrosis occurs early in treatment especially in patients who have protein C or S deficiency. The latter are natural anticoagulants also depending on vitamin K for synthesis. Initial treatment with warfarin therefore results in a reduced concentration of the body's own anticoagulants. In such cases, warfarin should be stopped and heparin started.
- 'Purple' toe syndrome is used to describe an acute digital cyanosis secondary to microembolism from a proximal atheromatous source and is common in patients with atherosclerotic disease such as diabetes mellitus, hypertension and peripheral vascular disease. Following such an episode, warfarin should be contraindicated.

Other rare adverse effects include:^{1,16,21}

- alopecia
- urticaria, dermatitis
- nausea, diarrhoea and abdominal cramps
- anorexia
- unexplained drop in haematocrit
- jaundice, hepatic dysfunction and pancreatitis.

Contraindications

Contraindications (listed below) depend on individual circumstances and are seldom absolute. It is recommended that an individual's risk/benefit assessment is performed prior to initiating warfarin, and then annually.^{1,16,19,21,22}

The following may be considered as **absolute** contraindications:^{16,19,22}

- Pregnancy. Due to the teratogenic effects of warfarin, patients receiving warfarin should be warned about the risks prior to

conception. Patients who conceive while on warfarin should be advised to seek immediate expert help.

- Bleeding predisposition such as haemophilia
- Thrombocytopenia (<50 x 10³/μl)
- Uncontrolled hypertension (>160/90). However, this may be considered as reversible if hypertension is adequately treated
- Noncompliance to medication or monitoring.

The following may be considered as **relative** contraindications:^{19,22}

- Significant alcohol use (more than 28 units per week for men; more than 21 units for women)

- Conventional NSAID use leading to a greater risk of gastrointestinal bleeding - this may be considered as reversible if replaced with alternative therapy that will allow the patient to take anticoagulants
- Trauma related activities.

This review summarises the numerous factors that may affect the body's handling of warfarin. As the use of warfarin increases and patients' regimens become more complex, maintaining patients' blood levels within the therapeutic range becomes more challenging, with bleeding the major feared adverse effect to prevent. The advent of near patient testing with the availability of immediate INR results, may be the solution to making treatment with warfarin safer in the future.

Annex 1

Useful sources of information

Source	Short Description
Stockley Drug Interactions – A Pharmaceutical Press Publication, 2005	General information related to anticoagulant interactions
Herbal Medications – A Pharmaceutical Press Publication, 2005	Individual drug monographs discuss current evidence. Particularly useful are Appendices 6 and 17 that refer specifically to oral anticoagulants
www.bnf.org	Latest version of British National Formulary – suitable source for warfarin-drug interactions
www.mca.gov.uk	Site for the Medicines and Health Care Regulatory Authority, UK – a useful source of any newly reported interactions between alternative therapies and warfarin
www.fda.gov/medwatch	FDA, USA, safety information and adverse event reporting programme
www.drugs.com	Physician's Desk Reference Information requiring a free first time registration. Exhaustive information on warfarin including interactions and endogenous factors influencing metabolism of the drug
British Society of Haematology www.bcshguidelines.com	Guidelines on Oral Anticoagulation: third edition, 1998
Scottish Intercollegiate Guideline Network www.sign.ac.uk	Antithrombotic Therapy (No.36), March 1999

References

1. Warfarin in practice: A pharmacists' guide to oral anticoagulants in primary care. NES Education for Scotland (Pharmacy). 2004
2. Clinically significant warfarin and drug interactions. University of Washington Medical Centre Anticoagulation Clinics. July 2002.
3. Adams P. Drug Interactions that matter: Warfarin. *Pharm J* 1998; 261:704-8.
4. Hirsh J, Dalen JE, Anderson DR, Poller L, Bussey H, Ansell J et al. Oral anticoagulants: mechanism of action, clinical effectiveness and optimal therapeutic range. *Chest* 2001; 119:8-21.
5. Horn JR, Hansten PD. Enhanced warfarin response and antibiotics. *Pharmacy Times* June 2004. www.hanstenandhorn.com. Cited: 30th August 2005.
6. Stockley IH (Ed). *Drug Interactions*. London: Pharmaceutical Press. Electronic Version (6th Edition [2005]).
7. Ramsay NA, Kenny MW, Davies G, Patel JP. Complimentary and alternative medicine use among patients starting warfarin. *Br J Haematol* 2005;130:777-80.
8. Wong RSM, Cheng G, Chan TYK. Use of herbal medicines by patients receiving warfarin. *Drug Safety* 2003; 26(8):585-88.
9. Heck AM, Dewitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. *Am J Health-Sys Pharm* 2000;57(13):1221-27.
10. Stenton SB, Bungard TJ, Ackman ML. Interactions between warfarin and herbal products, minerals and vitamins: A Pharmacist's Guide *CJHP* 2001;54(3): 186-92.
11. Barnes J, Anderson LA, Philipson JD. Herbal Therapeutics (10) Herbal Interactions. *Pharm J* 2003;270:118-21.
12. Potential warfarin interactions with dietary supplements. University of Washington Medical Centre Anticoagulation Clinics. July 2002.

Practice Points

Aiding safe management of patients on warfarin

- Almost any drug may interact with warfarin.
- Where possible, an interacting drug should be changed for a therapeutically equivalent non-interacting drug.
- When in doubt, check with a suitable source of information
- Patients who are on multiple drug therapy are more prone to an unpredictable response.
- Monitoring is more important during introduction, discontinuation and dosage adjustments of potentially interacting drugs.
- If the drug change lasts < 5 days, either no change in dose, a minor dose reduction or omission of one complete dose of warfarin may be recommended.
- If the drug change lasts > 5 days, it is advisable to check INR one week after the start of the new drug and adjust the warfarin dose on basis of result.
- Where no information about drug interaction is available, one should repeat INR within 4-7 days after starting or stopping treatment.

13. Physician's Desk Reference Information. Warfarin Sodium. www.drugs.com. Cited 8th April 2006.
14. Mason P. Food-Drug Interactions: Nutritional supplements and drugs (2). *Pharm J* 2002;269:609-11.
15. Mason P. Drug-Food Interactions: Food and Medicines (1). *Pharm J* 2002;269: 571-73.
16. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. www.bnf.org. Cited 8th April 2006.
17. Brigden ML, Kay C, Le A, Graydon C, McLeod B. Audit of the frequency and clinical response to excessive oral anticoagulation in an out-patient population. *Am J Haematol* 1998;59:22-7.
18. Levine MN, Raskob G, Landefeld S, Hirsh J. Haemorrhagic Complications of Anticoagulant Treatment. *Chest* 1995;108 (Suppl 4):276S-90S.
19. Man-Son-Hing M, Laupacis A. Anticoagulant-related Bleeding in Older Persons with Atrial Fibrillation. *Arch Int Med* 2003;163:1580-6.
20. Oden A, Fahlen M. Oral anticoagulation and risk of death: a medical record linkage study. *BMJ* 2002;325:1073-5.
21. Wittkowsky Ann K. Thrombosis. In: Young LY, KodaKimble MA. *Applied Therapeutics: The Clinical use of drugs*. 6th edition. Vancouver. Applied Therapeutics. 1995.
22. Sudlow M, Thomson R, Thwaites B, Rodgers H, Kenny RA. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. *Lancet* 1998;352: 1167-71.

Erratum

Vella V. Drug-induced peptic ulcer disease. *Journal of the Malta College of Pharmacy Practice* 2005;10:16. The fifth sentence in the second paragraph under the sub-heading 'Bisphosphonates' should have read: Patients should be also be reminded to stand or sit upright for at least 30 minutes after taking the tablet.