Managing variability in warfarin dosing:
Drugs, diseases and diets

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If one were to ask general practitioners, or pharmacists or nurses, to name a drug that was difficult to manage, most likely the answer would be warfarin. This, of course, is not a surprise. Warfarin is a potent drug with a potentially dangerous pharmacological effect; it has a narrow therapeutic window between ineffectiveness and toxicity; it displays wide inter- and intra-individual variation in effect; and it is prone to many external influences on its therapeutic effect from drug–drug interactions, patient co-morbidities and variable dietary intake. Add to this the inconvenience of regular monitoring and the effects of non-adherence or miscommunication between patient and practitioner and there is a ready recipe for trouble.

Pharmacology of warfarin

Warfarin produces its anticoagulant effect by interfering with the synthesis of vitamin K–dependent clotting factors. By interrupting the cyclical conversion of vitamin K to its 2,3 epoxide, warfarin, in turn, prevents the γ (gamma) carboxylation of the coagulation factors II, VII, IX and X. The resulting decarboxylated, or only partially carboxylated, proteins exert a lesser or no coagulant effect. It should also be noted that warfarin also prevents the carboxylation of proteins C and S and thereby has the potential to be procoagulant although in most situations the anticoagulant effect is dominant.[1]

Warfarin is most commonly prescribed as a racaemic mixture of the two optical isomers S-warfarin and R-warfarin. The S-isomer is the more potent anticoagulant, being five to six times more active that R-warfarin.[2] Both are rapidly and almost completely absorbed from the GI tract. They circulate, bound to plasma proteins, to the liver where they are metabolised via separate pathways; the S-isomer is metabolised via cytochrome P450 (CYP) isoenzyme 2C9 whilst the R-isomer is metabolised by CYP3A4, CYP1A2 and CYP2C19.[3]

As mentioned above, there is a wide variation, up to 20-fold, in anticoagulant response to a given dose of warfarin between different patients.[1] This variation is due, in part at least, to genetic polymorphisms that affect both the pharmacodynamics of warfarin and its pharmacokinetics. Two genetic variants of CYP2C9 have been shown to reduce the metabolism of warfarin by between 30% and 80%, leading to an increased risk of bleeding.[4] Genetic variants of vitamin K epoxide reductase complex subunit 1 (VKORC1) have also been identified and grouped to predict dose requirements.[5] Linear regression models that have used CYP2C9 and VKORC1 alongside age, weight, smoking status and other drug use can account for approximately 50% of the inter-individual variability seen with warfarin.[6]

Whilst this is very useful information and may help when initiating new patients on warfarin, it does not explain the intra-individual variation that is more difficult to manage. This fluctuation in anticoagulant control is more commonly due to drug–drug, drug–disease or drug–food interactions. In the category drug–drug interactions one should always consider those drugs that are complementary, alternative or herbal remedies that are often perceived as being without adverse effects. In the category of drug–food interactions one should also consider the dietary supplements that are now becoming so popular.

Drug–interactions with warfarin

Prescribing guides, pharmacy and pharmacology textbooks of drug–drug interactions for the most part are unhelpful to the practitioner who needs to discriminate the theoretical from the actual and important. The data on drug–drug interactions are usually from one of two sources, either pharmacological studies of CYP interactions or case reports. Pharmacological studies may be either in vitro models using 'probes' to identify common metabolic pathways and therefore suggest the potential for interaction or in vitro studies, usually in healthy volunteers, demonstrating an interaction. Neither is ideal since healthy volunteers do not often turn up in the surgery! Case reports are much more helpful, but suffer from the inability to necessarily extrapolate from one individual with a particular set of often peculiar and unique parameters and genotypes, to the patient whom you have sitting in front of you.

It was hoped that computerisation would be valuable in providing clinical decision support either through automated alerts or quick reference guides. A number of these are available and they are increasingly able to rank the likelihood and severity of the potential interaction. For the most part, however, they have a limited ability to discriminate between the theoretical and the real.[7–11] Worse still, early iterations of the software produced a deluge of inappropriate warnings about drug interactions, frustrating the practitioner to the extent that they either developed 'alert fatigue' and ignored them or simply turned the software off.[12] Conversely, there is also a risk involved in the use of very good software; there is a danger that we become so reliant on it that we do not think about the non-prescription drugs that the patient is taking and therefore fail to identify a potential problem.

In order to best reduce the risk of harmful drug interactions, what is needed is prescribers with a good understanding of the potential for drug interactions, some knowledge about how they might manifest, and a pragmatic, commonsense approach to monitoring and dose adjustment.

Drug–drug interactions with warfarin may be either pharmacodynamic or pharmacokinetic interactions. They may occur by one of a number of mechanisms including reduced absorption, displacement from protein binding sites, increased hepatic clearance, reduced hepatic clearance, impaired synthesis of vitamin K, interruption of the vitamin K cycle, direct injury to the gastrontestinal tract or interference with platelet function. It should also be noted that a number of drugs have multiple modes of interaction.

For those who would like a comprehensive review of the data on warfarin drug interactions, these do exist in the literature.[13–17] The discussion here is limited to those interactions of more significance that might be seen frequently in general practice.

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As a rule, practitioners should be discouraged from using mnemonics and aide-memoires where drug–drug interactions are concerned. It is too easy to forget important ones and there are too many exceptions; really one should check. However, a commonly used model is 'the 8As': antibiotics; antifungals; antidepressants; antiplatelets; amiodarone; anti-inflammatories; acetaminophen (OK that's a P – paracetamol) and alternative remedies.

Antibiotics, almost all of them, have been reported to interact with warfarin. For the most part the re-

Key Points

- Variability in the reported INR is normal. This may be the result of limitations around the measurement reliability of the test, or of subtle changes in diet or exercise and requires monitoring but no action unless the patient is at risk of either bleeding or thromboembolic events; i.e. substantially above or below their target INR.
- Clinically important changes in the INR may reflect changes in drugs, adherence, diet or co-morbidities.
- Drug–drug interactions with warfarin are widely reported, are manifest through a variety of mechanisms and are often unpredictable in both their occurrence and the magnitude of the effect.
- Where possible drugs with a well-established record of interaction should be avoided. Where alternatives to interacting drugs are not available, or are inferior, the interacting drug may be prescribed and the INR more closely monitored.
- Where there is intercurrent illness or a worsening of conditions with the potential to impact on liver function, such as congestive heart failure, the INR should be more closely monitored until the patient is stabilised.
- Patients should be counselled clearly on the potential for interaction between warfarin and other medicines, whether prescribed, over-the-counter, traditional, herbal or complementary. Patients should be encouraged to discuss their use of other medicines rather than being told to avoid them.

ported mechanism is a reduction in vitamin K_2 synthesis by gut flora, thereby further reducing the synthesis of vitamin K–dependent clotting factors and increasing the INR. Whilst predictable, the occurrence is very variable. Antibiotics to be particularly aware of include metronidazole, ciprofloxacin, norfloxacin and the macrolides (erythromycin, roxithromycin and clarithromycin). These antibiotics also inhibit CYP2C9 and therefore inhibit the metabolism of warfarin increasing its effect. Other antibiotics worthy of a mention are rifampicin and co-trimoxazole. Rifampicin is a potent CYP2C9 enzyme inducer, which therefore increases the metabolism of S-warfarin, reducing the INR and *potentially* risking a thromboembolic event if the INR falls below 1.8 for any length of time. Co-trimoxazole is a combination of sulfamethoxazole and trimethoprim, both of which have been reported to affect warfarin metabolism and may also cause displacement of warfarin from its protein binding sites, the net effect being an increased INR. Trimethoprim alone appears to have a modest effect, but the combination should be monitored closely.

Antifungals inhibit the metabolism of warfarin and can cause a pronounced rise in the INR, with associated bleeding risk. In particular the evidence of an interaction is strong for fluconazole and miconazole. The interaction occurs with both oral and vaginal miconazole. Where antifungals are co-prescribed with warfarin it is strongly advised that the INR be monitored more frequently.

Antidepressants, particularly the SSRIs, have been reported to increase the INR, due to inhibition of CYP enzyme activity, but also increase the risk of bleeding in the absence of a raised INR, this is thought to be due to a direct antiplatelet effect.

Antiplatelets, including aspirin, are a particularly difficult group to manage. Whilst there is no debate about the increased risk of bleeding with aspirin at anti-inflammatory doses, there remains a difference of opinion regarding the relative risk–benefit of low dose aspirin. Clinical trials and meta-analyses are broadly supportive of the view that although there is an increased risk, the benefits outweigh the risk in those with a clear indication for aspirin.[18-21] However, there is conflicting data from a recent analysis of the United Kingdom General Practice Database, which suggests that outside the comfortable confines of clinical trials there may be an excess of bleeding events.[22] Whilst a study of this type certainly has biases of its own, it certainly does provide pause for thought and, although the decision is no easier to make, suggests that we do need to reassure ourselves that the benefits of co-prescription are indeed justified since the bleeding will not be associated with a high INR or, in most cases, any other kind of warning.[23]

Acetaminophen (paracetamol) is a frequently unrecognised cause of over-anticoagulation

Anti-arrhythmics, specifically amiodarone, inhibit the metabolism of warfarin, thereby increasing the INR. Most patients are affected and the rise can be dramatic, ultimately requiring a warfarin dose reduction of 30–50%. This interaction, though predictable, can be very difficult to manage. Because of amiodarone's extremely long half-life there may be a slow onset of the interaction (10–14 days) and a very slow off-set of effect of weeks to months if the amiodarone is stopped and the warfarin continued. Whilst amiodarone is, perhaps, not the antiarrhythmic of first choice for most patients with AF, it is commonly used and these patients are, of course, very likely to be co-prescribed warfarin. Quinidine is rarely used now but, again, has the potential to cause a rise in the INR.

Anti-inflammatories such as the NSAIDs and COX-2 inhibitors are associated with an increased bleeding risk, particularly GI, in the absence of a raised INR. There are reports of some COX-2 inhibitors causing a significant increase in the INR. Patients who are at highest risk of bleeding, including the elderly, should be closely monitored if COX-2 inhibitors, in particular, are to be used. Other analgesics, such as tramadol, have also been reported to cause a significant increase in the INR; there is a suggestion that this is related to a specific genotype interaction with CYP2D6.[24]

Acetaminophen (paracetamol) is a frequently unrecognised cause of over-anticoagulation. The proposed mechanism is the poisoning of vitamin K–dependent carboxylase by a paracetamol metabolite thereby disrupting the vitamin K cycle and preventing the formation of the vitamin K–dependent clotting factors.[25] Whilst infrequent 'when required' dosing is unlikely to be problematic, there is consistent evidence that regular, full dose paracetamol causes a rapid and clinically significant increase in the INR in some patients. Care should be taken and additional monitoring undertaken when initiating or discontinuing regular paracetamol.

Alternative remedies are an absolute minefield, simply because of the lack of information for many. There is data on a number of the more commonly used herbal or traditional Chinese medicines, but little for most others.[14-16, 26-28] An increased risk of bleeding has been linked to the use of CAMs.[29] The investigation of drug–herb and drug–supplement interactions is further hampered by the variability both between and within products. Many products do not have the same consistency of active ingredients seen in pharmaceuticals. Those that are known to interact and that require particular attention are St John's wort, fenugreek, dong quai, ginkgo biloba, garlic and ginseng. All except St John's wort and ginseng have been shown to increase the INR;

ginseng appears to be an enzyme inducer and therefore, like St John's wort, causes a decrease in the INR.

The Committee on Safety of Medicines in the UK has recommended that St John's wort should be avoided in patients taking warfarin.

To briefly add to the list of the 8As, one should also consider the *anticonvulsants*, particularly carbamazepine, phenobarbitone, primidone, phenytoin and sodium valproate. Classically, carbamazepine, phenobarbitone and primidone are enzyme inducers and therefore will lower the INR. Sodium valproate inhibits the metabolism of warfarin and increases the INR. Frustratingly, phenytoin has been shown to cause an increase in the INR followed by a later decrease as the liver enzymes are induced and clearance increased. For the most part, anticonvulsants are a long-term treatment and, once dosing is stable, do not cause ongoing problems with warfarin control. However, it is important to consider their interactions when starting, stopping or modifying dosages.

Another, rather tricky 'A' is for the anti-gout drugs allopurinol and colchicine. Both cause an increase in the INR and risk of bleeding, and in both cases it is rare and unpredictable but clinically significant. The best advice is to monitor the INR closely when starting, stopping or radically altering doses.

Having run out of 'As', the remaining 'odd' ones to consider are lipid lowering drugs, hormones and 'anti-obesity' drugs. For the most part these interactions are benign, but there have been reports of increased INRs for most of the statins and bezafibrate. Cholestyramine, thankfully rarely prescribed, may cause a reduction in vitamin K absorption or in warfarin absorption and may therefore unpredictably increase or decrease the INR. It appears that relatively few patients are affected and, again, co-administration is chronic and therefore can easily be worked around by increasing monitoring for

Table 1. The 8 As (plus one) – drugs that commonly interact with warfarin

Drug or drug class	Risk of bleeding	Mechanism of interaction
Antibiotics		
Most agents Of note: co-trimoxazole, metronidazole, macrolides, quinolones	Increased	Alteration in the gut flora and reduced bacterial synthesis of vitamin K_2 and/or inhibition of hepatic warfarin metabolism
Rifampicin	Decreased	Induction of CYP2C9
Antifungals		
Fluconazole, miconazole	Increased	Inhibition of CYP2C9
Antidepressants		
SSRIs	Increased (INR may not be raised)	Antiplatelet effects and/or inhibition of CYP2C9
Antiplatelet agents		
Aspirin, clopidogrel and dipyridamole	Increased (INR not raised)	Antiplatelet effects
Antiarrhythmics		
Amiodarone	Increased	Inhibition of CYP2C9
Anti-inflammatory agents		
NSAIDs and COX-2 inhibitors	Increased (INR may not be raised)	Direct mucosal injury, antiplatelet effects, inhibition of CYP2C9 suggested for some COX-2
Acetaminophen		
Paracetamol	Increased	Direct interference with vitamin K cycle Only significant with chronic dosing
Alternative remedies		
Ginkgo biloba, dong quai, fenugreek, garlic	Increased (INR may not be raised)	Poorly understood, may include antiplatelet effects and inhibition of metabolism
St John's wort, ginseng	Decreased	Poorly understood, may include inhibition of metabolism
Anticonvulsants		
Carbamazepine, phenobarbitone, primidone and phenytoin (late)	Decreased	Induction of CYP metabolism
Phenytoin (early) and sodium valproate	Increased	Inhibition of CYP metabolism

a week or so around initiation and discontinuation of the interacting drug. Thyroxine may increase the elimination of warfarin, as does hyperthyroidism, decreasing the INR. Carbimazole has the opposite effect. Careful control of the euthyroid state eliminates the need for concern. Hormone antagonists, such as tamoxifen and flutamide, are well established interacters and usually require a reduction in warfarin dose, up to a halving of the dose. Oestrogens and progestrogens do not directly affect the INR, but one should consider their use carefully in patients with a hypercoaguable state since they antagonise the effects of warfarin. Finally, the anti-obesity drugs orlistat and sibutramine have been implicated in loss of anticoagulant control, although pharmacokinetic studies with orlistat seem to indicate no effect, there is a certain logic given that vitamin K is a fat soluble vitamin and orlistat reduces fat absorption. Closer monitoring of the INR if initiating orlistat in patients already on warfarin is advisable.

Dietary vitamin K

Dietary intake of vitamin K is clearly a source of potential difficulty. Since vitamin K_1 can be directly incorporated into the vitamin K cycle before the relatively warfarin insensitive vitamin K reductase pathway, its impact, antagonising the effects of warfarin, is substantial. Vitamin K is largely sourced from green vegetables, although it is also found in a range of other foods. A list of foods and their vitamin K content is available online.[30] Food supplements, particularly enteral feeds, may also contain substantial amounts of vitamin K.[13] Given the seasonal nature of many people's diets, particularly the more elderly patients, one should always consider dietary changes for any unexplained fluctuation in the INR.

The administration of warfarin increases the sensitivity of people to small fluctuations in their vitamin K intake. Vitamin K is not stored in large quantities and people who are overly sensitive to the effects of warfarin, leading to brittle control, may benefit from vitamin K supplementation. Although this is a relatively new approach, there has been success in co-administration of small doses of vitamin K to patients on warfarin to assist in 'smoothing' out their INR response.[31]

Smoking and drinking

Whilst it is good practice to counsel against smoking and binge drinking for all patients, there is particularly good reason to do this in patients on warfarin. Smoking causes enzyme induction and therefore potentially lowers the INR. This is only of significance when the patient is either stopping smoking or, unfortunately, relapsing from a quit attempt. In these situations the effect on the INR is likely to be relatively small and picked up on routine monitoring, although increasing the frequency of testing in poorly controlled patients is probably advisable. Alcohol is variously sold to patients as 'not an issue' or 'abstain at all costs'. The truth is probably somewhere in between. Most patients with a steady and modest alcohol consumption can be left to enjoy life. Binge drinking leads to a cycle of enzyme inhibition and high INRs, often very high, followed by normalisation. Chronic alcoholism, on the other hand, leads to an enzyme induction but, given that it is chronic, is rarely a problem for warfarin management until the liver becomes cirrhotic.

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A practical approach to managing interactions

The reality of patient management is that combinations of interacting drugs are frequently unavoidable. However, this does not need to be hugely problematic for either patient or prescriber. Whilst it is difficult to predict the existence of an interaction or its magnitude for any given individual, it is, based on an understanding of the mechanism of the interaction, the half-life of the drugs involved and the half-life of vitamin K–dependent clotting factors, possible to fairly accurately predict the onset and offset of the interaction. It is therefore possible to plan an INR testing schedule that will identify any problems that do arise and allow you to respond to it.

Generally speaking, one only needs to worry about interactions when starting, stopping or modifying the dose of the interacting drug. If the interacting drug is to be used for a relatively short period of time – less than five to seven days – then it is reasonable to check the INR after two to three days. If the INR increases substantially it may be appropriate to omit a dose of warfarin or, if the INR falls significantly and the risk of a thromboembolic event is significant, supplement with a single small dose (30–50%).

If the co-administration is likely to be longer than five to seven days, then a temporary increase in the frequency of testing is appropriate, starting two to three days after the interacting drug is initiated with both the warfarin dose adjustment and frequency of monitoring guided by the response. A similar approach can be taken when stopping an interacting drug.

The key to stable warfarin control is, as with everything else, a careful history, a good instinct, a fair wind and a light hand on the tiller. Happy sailing!

Competing interests

None declared.

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Bisphosphonate therapy linked to risk for severe musculoskeletal pain

'Temporary or permanent discontinuation of bisphosphonate therapy should be considered in patients who present with severe musculoskeletal pain, the US Food and Drug Administration (FDA) warned healthcare professionals yesterday [7 January 2008]. Overlooking bisphosphonate therapy as a causal factor may delay diagnosis, thereby prolonging pain and/or impairment and the use of analgesics. In contrast with the acute-phase response that sometimes accompanies initial exposure to bisphosphonate therapy, some patients experience severe and sometimes incapacitating bone, joint, and/or muscle pain that begins months or years later.'

Waknine Y. Bisphosphonate Therapy Linked to Risk for Severe Musculoskeletal Pain. Medscape Medical News. http://www.medscape.com/viewarticle/568424?src=mp Accessed 17 January 2008.