Information for Pharmacists on Managing Warfarin Drug Interactions

Established and clinically important interactions.

DRUG	INTERACTION
Anabolic steroids + related drugs (e.g. Danazol)	Increased anticoagulant effect and bleeding seen. Avoid concurrent use. If this is not possible, close monitoring of INR is advisable if danazol is added to established anticoagulant regime; dose of warfarin should be reduced accordingly.
Amiodarone	Anticoagulant effect may be significantly increased. Bleeding may occur if warfarin dose not reduced appropriately. The interaction begins to develop within a few days and is usually maximal by 2 to 7 weeks. Interaction may persist for several weeks after amiodarone is stopped. Monitor INR closely and consider reducing the dose of warfarin by $^1/_3$ up to $^2/_3$ if amiodarone is added to already established anticoagulant regime.
Barbiturates (+ Primidone)	Anticoagulant effect reduced. Full therapeutic anticoagulation may only be achieved by a 30-60% increase in warfarin dose. The interaction occurs within 2-4 days, with maximal effect after 3 weeks. Monitor INR and increase dose accordingly.
Carbamazepine	Metabolism of warfarin is increased by carbamazepine leading to reduced anticoagulant effect. Monitor INR if carbamazepine added to patient established on warfarin and consider dose increases as appropriate.
Co-trimoxazole	Increased anticoagulant effect and bleeding. High incidence of interaction. Warfarin dose should be reduced and INR well monitored.
Cranberry Juice	Increased anticoagulant effect, in some cases marked. Avoid concomitant use unless health benefits outweigh risk. See CSM advice October 2004.
Fibrates	Increased anticoagulant effect. In some cases severe bleeding has been seen. Incidence of interaction 20-100%. Warfarin dose reductions of $^1/_3$ to ½ may be needed to avoid bleeding. Monitor INR closely.
Fluconazole	Increased INR and bleeding. Monitor levels well and gradually reduce warfarin dose appropriately (approx. 20% reduction required with 50mg fluconazole daily, ranging to a 70% reduction with 600mg fluconazole daily).
Fluorouracil and related prodrugs (e.g. capcitabine)	Increased INR and anticoagulant effects. Several reports of overcoagulation. Prothrombin times and INR should be regularly monitored, with possible need to reduce dose of warfarin.
Metronidazole	Anticoagulant effects of warfarin can be markedly increased. Monitor INR and adjust warfarin dose accordingly.
Miconazole	Anticoagulant effects markedly increased (bleeding can take 15 days to develop, raised INR can occur within 3 days). Oral miconazole should not be given unless INR closely monitored and suitable dose reductions made (usually halving). Interaction is also seen with oral gel, and has also been reported after vaginal administration. Monitoring required for all routes.
Rifampicin	Anticoagulant effects markedly reduced. Seen within 5-7 days and persists for 2 to 5 weeks after withdrawal. Warfarin dose may need to

	be doubled or trebled, and then reduced by equivalent amount following withdrawal of rifampicin.
St John's Wort	Moderate reduction in anticoagulant effect Avoid concomitant use since amount of active ingredient may vary in St John's Wort products. see CSM advice.
Sulfinpyrazone	The anticoagulant effect of warfarin is markedly increased and serious bleeding has occurred. If used concurrently monitor INR well and reduce warfarin dose, possibly by half.
Sulphonamides	High incidence of interaction with co-trimoxazole. Warfarin dose should be reduced and prothrombin times well monitored. Little information with other sulphonamides but advice should be as for co-trimoxazole.
Tamoxifen Toremifene	Anticoagulant effect markedly increased (bleeding has occurred). Clinically important, affects some but not all patients. Monitor INR closely and reduce warfarin dose by ½ to $^{2}/_{3}$.
Testosterone	Increased anticoagulant effect and bleeding has been seen. Bleeding may occur if warfarin dose not reduced. Interaction develops within 2-3 days. If concurrent use cannot be avoided reduce warfarin dose and monitor INR closely.
Voriconazole	Voriconazole increases the anticoagulant effect of warfarin. The manufacturer therefore advises close monitoring of the prothrombin time in any patient on an oral anticoagulant who is given voriconazole. Dose adjustments of the anticoagulant should be made accordingly.

Moderate Interactions

DRUG	INTERACTION
Allopurinol	Anticoagulant effect possibly enhanced. Few case reports of important interaction. Nevertheless, monitor INR of any patient when allopurinol first added.
Aspirin	Aspirin has direct GI irritant effect. Increased risk of bleeding due to antiplatelet effect. Avoid analgesic/anti-inflammatory doses of aspirin. Interaction with low dose aspirin (75-150mg daily) is of much lower risk but risk/benefit needs assessing in each case.
Colestyramine	Anticoagulant effect may be reduced. Clinical importance uncertain, avoid concurrent use if possible. If given concurrently monitor INR closely. Warfarin should be given 1 hour before or 4 to 6 hours after colestyramine
Ciclosporin	Effects of warfarin may be increased or decreased and ciclosporin levels may be reduced. As the interaction outcome is unpredictable advice is that INR and ciclosporin levels are monitored closely during concomitant use and dosage of either drug adjusted according to levels.
Cimetidine	Increased anticoagulant effect, bleeding in some patients seen with days. Response should be monitored in every patient when cimetidine is first added, being alert for the need to reduce the warfarin dosage.
Ciprofloxacin	Bleeding has occurred unpredictably in isolated cases therefore prudent to monitor when first added.
Clarithromycin	Established and unpredictable interaction. Marked increase in effects of warfarin seen in a small number of patients. Concurrent use need

	not be avoided but advisable to monitor, especially high-risk categories (e.g. elderly)
Clopidogrel	Manufacturer advises concurrent use not recommended as clopidogrel+ warfarin may increase the intensity of bleeding. Some limited evidence of safety.
Cytotoxics	Anticoagulant effect possibly enhanced by capecitabine, carboplatin, cyclophosphamide, doxorubicin; etoposide, 5-fluouracil, gemcitabine; ifosfamide; methotrexate; procarbazine; vincristine and vindesine. Anticoagulant effect reduced by azathioprine and 6-mercaptopurine. Dose of anticoagulant may need adjustment.
Disulfuram	Anticoagulant effects of warfarin increased. Will occur in most patients. Monitor INR closely and adjust warfarin dose. Note: Use smaller warfarin loading dose in patient's already on disulfuram.
Erlotinib	Increased risk of bleeding, closely monitor INR.
Erythromycin	Established and unpredictable interaction. Marked increase in effects of warfarin seen in a small number of patients. Concurrent use need not be avoided but advisable to monitor, especially high-risk categories (e.g. elderly)
Glucosamine	Anticoagulant effect of warfarin enhanced. BNF advises avoid concomitant use.
Itraconazole	Isolated reports of marked increases in anticoagulant effect accompanied by bruising and bleeding. It would be prudent to increase monitoring of the INR.
Leflunomide	May increase INR and bleeding. Isolated case reports. It would be prudent to increase monitoring of the INR.
Nevirapine	Nevirapine may decrease the anticoagulant effect of warfarin. It would be prudent to monitor prothrombin times and INRs in any patient if warfarin and nevirapine are used concurrently, being alert for the need to increase the warfarin dosage (possibly twofold).
Norfloxacin	Bleeding has occurred unpredictably therefore prudent to monitor when first added.
NSAID (+COX 2s)	All NSAIDS/COX2s cause GI irritation. NSAIDs reduce platelet aggregation that can worsen bleeding events. Some NSAIDs may enhance anticoagulant effect. Less likelihood of interaction with ibuprofen. If need to co-prescribe with warfarin then monitor for GI toxicity/bleeding and monitor INR. Use lowest dose of the safest NSAID and consider gastroprotection prophylaxis with proton pump inhibitor.
Penicillins	Effects of oral anticoagulants are not normally altered. However, isolated reports of increased bleeding have been reported. The BNF therefore advises that INR should be monitored to identify occasional and unpredictable cases.
Phenytoin	Possibility of increased or decreased anticoagulant effect. Closely monitor both drugs.
Proguanil	Isolated case report of bleeding and increased prothrombin time after 5 weeks of proguanil.
Propafenone	Anticoagulant effect may be increased. Monitor INR closely and reduce warfarin dose as appropriate.
Protease Inhibitors	Both increases and decreases in anticoagulation have been reported. Interaction not well established.
Quinidine	Anticoagulant effect may be increased or decreased or be unaltered

	when quinidine taken. Monitor INR closely.
Quinolone antibiotics	Normally no interaction. However, bleeding has occurred unpredictably on patients on ciprofloxacin and norfloxacin, therefore prudent to monitor when first added.
Sibutramine	Increased risk of bleeding when given with warfarin.
SSRIs	Very occasional and unpredictable interaction, case reports of warfarin interaction with many of the SSRI's. Increased INR, it would be prudent to increase monitoring of the INR initially.
Sucralfate	Decreased anticoagulant effect possibly due to adsorption. Isolated case reports.
Thyroid Hormones	Increased anticoagulant effect and bleeding has been seen. Hypothyroid patients initiated on thyroid hormones will need downward adjustment of warfarin dose as treatment proceeds to avoid bleeding.
Venlafaxine	A very small number of reports of increased INR and bleeding.
Vitamin K*	Antagonises anticoagulant effect of warfarin. Dose of vitamin K at which this becomes clinically important appears to depend on the vitamin K status of the individual.
Zafirlukast	Increased anticoagulant effect. Limited reports. If given to patients stabilised on warfarin monitor INR well and be alert to the need to reduce warfarin dose.

*Some health foods, food supplements, enteral feeds, large quantities of green vegetables, seaweed, green tea can contain significant quantities of Vitamin K.

N.B. There are also numerous milder warfarin drug interactions with lower clinical significance. Additionally, some herbal medicines, vitamins and food supplements can interact with warfarin. Please contact Medicines Information on **extension 5471** for individual information on these situations.

Bibliography

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