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DRUG INTERACTIONS II: FREQUENTLY ASKED QUESTIONS

- ☞ Drug interactions with warfarin are common and frequently cause toxicity
- ☞ Drug interactions resulting in reduced efficacy should be considered in patients on oral contraceptives who experience breakthrough bleeding
- ☞ The risk of QT prolongation is potentiated by drug interactions, especially in vulnerable patients
- ☞ Any interaction that increases statin plasma levels greatly increases the risk of toxicity

INTRODUCTION

It is difficult to give an accurate estimate of the incidence of clinically relevant drug interactions, however, as discussed in the previous bulletin,¹ certain commonly used drugs are frequently implicated in drug interactions.² This second bulletin on drug interactions will deal with frequently occurring problems relating to potential drug interactions in clinical practice, for which the NMIC has provided practical guidance.

WARFARIN AND DRUG INTERACTIONS

Warfarin is one of the most widely used oral anticoagulants.^{3,4} Due to its narrow therapeutic range, small variations in plasma levels may result in bleeding or thrombotic complications,⁴ therefore patients prescribed warfarin are at particular risk of drug interactions.⁵

Most clinically relevant drug interactions reported with warfarin involve a small number of drug classes and a handful of mechanisms.⁵ The commonest **pharmacokinetic interaction** with warfarin involves the **inhibition or induction of its metabolism**.⁶ Warfarin consists of two isomers. The S-isomer is 5 times more potent than the R-isomer and is metabolised by CYP 2C9. Many of the drugs reported to potentiate warfarin's effect, are known inhibitors of CYP 2C9 including: amiodarone, fluconazole, fluvastatin and sertraline.³ The R-isomer is metabolised by CYP 1A2 (which is inhibited by quinolones) and CYP 3A4 (inhibited by macrolides).^{3,6}

Pharmacodynamic (PD) interactions occur less frequently; however they too influence the efficacy and safety of warfarin therapy. The commonest type is **concomitant use of warfarin with anti-platelet agents** including aspirin and other NSAIDs and clopidogrel.⁶ These agents can increase the bleeding risk without increasing the INR.⁶ There are numerous **herbal / alternative medications** which may also have anti-platelet effects but these interactions are less predictable; these include garlic, ginkgo, coenzyme Q-10, ginseng and papaya.⁶ The PD profile of warfarin may be influenced by medications that affect either vitamin K production (e.g. effect on gut flora by antibiotics) or interfere with the vitamin K cycle (e.g. high doses of paracetamol).⁷

Regular measurement of the INR with subsequent dose adjustment as appropriate, is particularly important when a patient is on medication(s), which may interact with the metabolism of warfarin. In addition, some drugs are associated with an increased risk of bleeding due to their own PD profile (e.g. aspirin, NSAIDs), leading to an additional increased risk of clinically relevant bleeds when a patient is also taking warfarin. **Patient education is important in ensuring safe use of warfarin. Patients should always be informed about the potential adverse consequences of taking other drugs, including OTC and herbal medications.**⁶

Which commonly used antibiotics interact with warfarin?

This represents one of the most common questions received by the NMIC, however available information is not always straightforward.

Macrolides: Several sources¹¹ note that **erythromycin** and **clarithromycin** may enhance the anticoagulant effects of warfarin.^{8,9,10} There also have been postmarketing reports of enhanced anticoagulation with **azithromycin**.¹¹ Although the effect of warfarin appears to be markedly increased by macrolides only occasionally, it is unpredictable; therefore it is recommended to increase monitoring in patients on warfarin when they are first given any macrolide and on withdrawal.^{9,12} With azithromycin consideration should be given to its long half-life and the fact that an interaction may possibly not become apparent until a couple of days after completion of a short course (e.g. 5 day course of azithromycin).¹²

Fluoroquinolones: The interaction between warfarin and quinolones, such as ciprofloxacin and norfloxacin, is deemed to be clinically significant with case reports of increased INR and bleeding.^{8,13,14} The mechanism of interaction is

uncertain and it is not clear what other factors may have been responsible in cases where the effects of the anticoagulant were increased. **Concurrent use need not be avoided but it is prudent to monitor the effects when quinolones are added to warfarin therapy**¹³ as adjustments of the warfarin dose may be necessary.¹⁴

Metronidazole: Concomitant use of warfarin and metronidazole may result in an increased risk of bleeding due to an increase in prothrombin time.¹⁵ This **interaction appears to be established and clinically important.** The mechanism of interaction is unknown, although suggestions include inhibition of S-warfarin metabolism by metronidazole.¹⁵ In cases of co-administration, INR should be monitored more frequently and anticoagulant therapy adjusted if necessary.¹⁶

Penicillins: There have been isolated reports of increased INR and/or bleeding.^{8,17,18} The mechanism is unknown but it has been suggested that penicillins reduce the production of gut flora thereby decreasing the production of vitamin K.¹⁹ Considering the frequency of prescribing of penicillins and given the relatively few reports of this interaction, it is likely that no clinically relevant interaction occurs with most penicillin usage. However, evidence from clinical studies has been conflicting, therefore it is recommended that concurrent use should be monitored.^{17,19}

Trimethoprim: Information is limited on an interaction with warfarin. Enhancement of anticoagulant effects has been suggested, though the clinical significance is unknown.^{8,20}

Summary of Advice: prescribers are always advised to check the Summary of Product Characteristics (SPC) of any antibiotic agent before prescribing it to a patient on warfarin. While interactions with quinolones or metronidazole are well documented, the possibility of an interaction with other antibiotics is unpredictable. Therefore if in doubt, the INR should be checked after introduction and also possibly on withdrawal of the antibiotic agent.

What is the nature of the interaction between warfarin and NSAIDs?

The combination of warfarin and NSAIDs, including aspirin, has been identified as a frequent potential source of clinically significant drug-drug interaction.²¹⁻²³ Evidence suggests **that combined use of NSAIDs and coumarin anticoagulants increase the risk of GI haemorrhage**, which is higher than that seen with either drug used alone.²⁴ A recent study showed a 4.6-fold increased relative risk of GI haemorrhage with the combination of warfarin and NSAIDs.²⁵ The risk of haemorrhage occurs with both selective and non-selective NSAIDs²⁴ and may occur at locations other than the GI tract.²⁶

Mechanism of action: the increased risk of haemorrhage is due to gastric irritation and inhibition of platelet aggregation by NSAIDs and the action of warfarin in inhibiting vitamin K.²⁶ There have also been case reports of some NSAIDs being associated with an increased INR, the magnitude of which varies with different reports.^{24,27} In addition there are people with variant CYP 2C9 (5-11% of Caucasians) who have a lower metabolising capacity for warfarin, who also experience an increased INR when on NSAIDs.²⁴

Summary of advice: It is recommended to avoid the concomitant use of NSAIDs and warfarin if simple analgesics can be used instead.²⁴ If a NSAID is considered necessary, the patient should be prescribed gastroprotection and consideration should be given to monitoring the patient's INR when initiating, changing the dose and discontinuing the NSAID.²⁷

PROLONGATION OF THE QT INTERVAL AND DRUG INTERACTIONS

The problem of drug-induced arrhythmias due to QT prolongation was highlighted in recent years by fatalities reported with the use of terfenadine (Triludan®) and thioridazine (Melleril®).²⁸ The QT interval represents the duration of cardiac ventricular depolarisation and subsequent repolarisation.²⁹ Anything that delays cardiac depolarisation will cause a prolongation of the QT interval; this creates an electrophysiological environment that favours the development of cardiac arrhythmias, including the potentially fatal torsades de pointes.²⁸

What is the link between drug interactions and the development of QT prolongation?

Table 1 outlines certain **patient factors**, known to be associated with a **longer QT interval** compared with the general population. In addition, **certain drug classes** are known to **prolong the QT interval** (Table 1).

Table 1: Risk factors in the development of prolonged QT interval²⁸⁻³⁰

Patient Risk Factors	Drugs Associated with QT prolongation
Extremes of age	Imidazoles
Female gender	Tricyclic antidepressants
CCF	Chlorpromazine, haloperidol
Electrolyte imbalance	Amiodarone / other anti-arrhythmic agents
Impaired hepatic function	Methadone (especially >100mg/day)
Impaired renal function	Erythromycin (IV ++)
	Some risk with oral erythromycin / clarithromycin
	Some risk with atypical antipsychotics*

* the Summary of Product Characteristics (SPC) gives product-specific information on QT prolongation for each medicine (www.medicines.ie; www.imb.ie)

Concomitant use of these agents or the inhibition of their metabolism / excretion by another drug (resulting in higher than recommended plasma levels) may increase the risk of significant QT prolongation and should be avoided. In addition, co-administration of one of these agents with any drug that results in hypokalaemia / hypomagnesaemia may also increase the risk of cardiac arrhythmia due to QT prolongation.²⁸⁻³⁰

Summary: Prolongation of the QT interval is associated with known predisposing patient risk factors as well as a number of drug classes. The risk increases if these drugs are co-administered, if their metabolism is inhibited by another drug or if the patient is predisposed to the development of QT prolongation while taking these drugs due to drug-induced electrolyte imbalance.

What role do drug interactions play in methadone-associated QT prolongation?

Methadone is a long-acting synthetic opioid used in the treatment of opioid addiction and chronic pain. The use of methadone is associated with a substantial reduction in mortality amongst treated versus untreated heroin users.^{31,32} However, there have been reports of QT prolongation and torsade de pointes associated with its use,³²⁻³⁵ although the prevalence remains unclear.³⁶

Methadone has a prolonged half-life and is subject to accumulation.³³ It is **extensively metabolised in the liver mainly by CYP3A4**; however other CYP enzymes are also involved including 2D6, 2C9, 2C19.³⁶ Consequently use with other drugs that induce or inhibit these CYP enzymes may result in changes in plasma concentration of methadone with potential toxicity.³⁶

Mechanism of action: Methadone binds to the cardiac ion channel *in vitro* and prolongs the action potential in a dose-dependent manner.³³ **Additional factors which contribute to QT prolongation in patients on methadone include: higher doses of methadone (>100mg/day), hypokalaemia, liver dysfunction and co-administration of CYP 3A4 inhibitors** including ciprofloxacin, fluoxetine, fluvoxamine, fluconazole, and some HIV agents including protease inhibitors.³²⁻³⁷

Summary of advice: Methadone is contraindicated in those with existing QT prolongation and should be used with caution in those at risk for the development of prolonged QT.³⁸ The Irish Medicines Board has recommended ECG monitoring for patients with recognised risk factors for QT prolongation who are on higher doses of methadone (>100mg/day).³⁷ Patients developing QT prolongation while on methadone should be evaluated for modifiable risk factors, including drug interactions (as outlined above).³⁸ Consideration should also be given to the possibility of concomitant illicit drug usage e.g. cocaine.³²

COMBINED ORAL CONTRACEPTIVES AND DRUG INTERACTIONS

Currently over 100 million women worldwide use the combined oral contraceptive pill (COC).³⁹ Efficacy can be reduced by a number of factors, including drug interactions, resulting in increased risk of an unplanned pregnancy.⁴⁰ Breakthrough bleeding (BTB) is sometimes the first clue to the possibility of a drug interaction.³⁹

What are the main methods of drug interaction affecting COC efficacy?

1. Induction of liver CYP enzymes by interacting drugs leading to increased elimination of oestrogen and progestogen can reduce considerably the efficacy of COCs.³⁹ The most **clinically important enzyme-inducing drugs** which interact with COCs include: rifampicin, rifabutin, griseofulvin, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, primidone, topiramate (>200mg/day), modafinil, some anti-HIV agents (e.g. nelfinavir, nevirapine, ritonavir) and St John's Wort.⁴¹ **Women on a COC and a short-term course of an enzyme-inducer require additional contraceptive precautions during treatment and for a further 7 days**; if there are less than 7 COC tablets left at the end of treatment, the next pill-free interval (PFI) should be missed.⁴² In women on a COC who require **long-term use of any enzyme inducer**, an alternative type of contraception should be considered. **Rifampicin** is a powerful enzyme inducer therefore, even if only taken for 2 days, **increased elimination by the liver should be assumed for 4 weeks** and extra contraceptive precautions taken during this time with the elimination of any PFIs.^{39,41}

2. Disturbance by antibiotics of the gut flora can result in reduced re-absorption of some reactivated oestrogen in a small minority of women.³⁹ While this may not affect COC efficacy, the UK Faculty of Family Planning advises that a **woman on a COC taking short courses (<3 weeks) of antibiotics that are not liver enzyme-inducing should use additional contraception during treatment and for an additional 7 days** (the PFI should be missed if there are less than 7 tablets left at the end of treatment).⁴³ This advice may be overly cautious for some antibiotics (e.g. co-trimoxazole and erythromycin), which can increase blood levels of oestrogen.

A woman on a COC who is prescribed a long-term antibiotic is advised to use additional contraceptive measures for 3 weeks and miss any PFI that is due. After 3 weeks, the bacterial flora develop anti-bacterial resistance and additional precautions are unnecessary unless a new antibiotic is prescribed.⁴¹ There is no concern for women on long-term antibiotics (for >3 weeks) who start a COC for the same reason.⁴¹

3. Other potential interactions: COC are themselves weak inhibitors of hepatic enzymes and they can lower the clearance of some drugs.³⁹ Ciclosporin levels can increase in patients on a COC therefore blood levels should be monitored to reduce the risk of toxicity.³⁹

4. COCs and anti-epileptic drugs: Most of the newer and some of the older (non-enzyme inducing) agents for epilepsy e.g. ethosuxamide, valproate and clonazepam, do not pose a COC-efficacy problem. **Lamotrigine** has been shown to modestly increase levonorgestrel clearance; effects on contraceptive efficacy are unknown, although the possibility of decreased contraceptive efficacy cannot be excluded. **Patients should be instructed to promptly report changes in their menstrual pattern**, i.e. BTB.⁴⁴ In addition, lamotrigine levels can be lowered by a COC, which may result in poor control of patients with epilepsy on lamotrigine commencing the COC.^{44,45} The SPC for lamotrigine gives clear guidance on how to initiate and adjust the dose of lamotrigine when starting or stopping hormonal contraceptives and this should be followed.⁴⁴ Consideration should be given to using contraception without a PFI, as first-line therapy (e.g. continuous hormonal contraceptives or non-hormonal methods).^{44,46}

ADDITIONAL DRUG INTERACTION QUESTIONS

What is the mechanism of drug interaction with statins?

Statins are among the most widely prescribed drugs in Ireland.⁴⁷ Although concerns have been raised in the media and elsewhere regarding their safety, the American Lipid Association recently undertook a review of all safety information from clinical trials and “real world” usage and concluded that statins demonstrated a very favourable benefit-risk relationship with respect to potential liver, muscle and kidney toxicity.⁴⁸ However, with all of the statins a threshold dose level exists, beyond which the risk exceeds the benefit. **Therefore, any interaction which interferes with the metabolism of a statin resulting in higher than expected plasma levels, increases the risk of toxicity.**⁴⁸

Mechanism of Action: Most of the drug interactions are due to interference with CYP 3A4 enzymatic activity. CYP 3A4 is involved in the metabolism of simvastatin and atorvastatin (see NMIC Drug Interactions Bulletin I)¹ therefore potential for such interaction can be anticipated. Table 2 outlines the metabolism of the commonly used statins in Ireland and potentially interacting medicines. Neither pravastatin nor rosuvastatin are metabolised by the CYP system to any great extent. However it is worthwhile noting that (a) **ciclosporin increases drug exposure for all statins**, (b) potent CYP 3A4 inducers may also reduce the activity of pravastatin and rosuvastatin in an unpredictable fashion and (c) **co-prescription of rosuvastatin with warfarin may result in an increase in INR.**^{49,50} The relevant SPC for each medicine contains up-to-date information on known and potential interactions and should be consulted if in doubt.^{49,50}

Table 2. Effect of commonly-used drugs on statin plasma levels⁴⁹⁻⁵⁴

Drug	Effect on statin plasma levels			
	Simvastatin	Pravastatin	Atorvastatin	Rosuvastatin
Imidazoles	↑↑↑	↔	↑↑↑	↔
Erythromycin / clarithromycin	↑↑↑	↑	↑↑↑	↔
Verapamil / diltiazem / amiodarone	↑↑↑	↔	↑↑↑	↔
Ciclosporin	↑↑↑	↑↑↑	↑↑↑	↑↑↑
Gemfibrozil	↑↑↑*	↑↑↑*	↑↑↑*	↑↑↑*
Grapefruit juice	↑↑↑	↔	↑↑↑	↑↑↑
Rifampicin / carbamazepine	↓	↓	↓	↓

↑↑↑ = >10-fold increased exposure to statin; ↑↑ = >5-10-fold and ↑ = ≤5-fold increased exposure; ↓ = reduced plasma levels of statin (variable)
↔ Levels practically unchanged.

* combination may result in myopathy, not primarily due to increased plasma levels of either drug

Is there an interaction between SSRIs/SNRIs and triptans?

Both the SSRI/SNRI antidepressants and the triptans (for migraine) have serotonergic activity. It has been suggested that concurrent use may result in “serotonin syndrome”, via a pharmacodynamic (additive effects on the serotonin system) or pharmacokinetic (inhibition of triptan metabolism via cytochrome P450 isoenzymes) interaction.⁵⁵ **Signs and symptoms of serotonin syndrome include restlessness, agitation, sweating, tremor and shivering, tachycardia, weakness, hyperreflexia and incoordination.** Although the potential for interaction between SSRIs and triptans exists, the weight of evidence suggests that concomitant use is normally uneventful.⁵⁵ However, the US FDA recently issued a warning based on a small number of reports of serotonin syndrome noted during concurrent use. Two reports described life-threatening events and in 13 reports the patients required hospitalisation.^{55,56} **The FDA recommended that patients treated concomitantly with a triptan and a SSRI/SNRI be informed of the possibility of serotonin syndrome (which may be more likely to occur when starting or increasing the dose of either agent) and be carefully followed.**

Summary of advice: In practice if both a SSRI and a triptan are clinically indicated, and if there are no contraindications from a regulatory aspect (see below), a pragmatic approach may be to use the combination with caution, in view of the potential for serious interaction, and to monitor for signs and symptoms of serotonin syndrome, particularly during treatment initiation, with dose increases, or with the addition of another serotonergic medicine. It is worth noting that while the SPCs for many of the SSRIs on the Irish market advise caution and close observation if combination with a triptan is warranted, some actually contraindicate the combination. It is recommended that prescribers check the up-to-date SPC for individual products.^{57,58}

SOURCES OF INFORMATION ON DRUG INTERACTIONS

- www.medicines.ie / www.imb.ie (access to Summary of Product Characteristics for all medicines)
- National Medicines Information Centre query answering service (contact details on page 1)
- British National Formulary (BNF) – Appendix 1
- www.medscape.com (drug interaction checker - free website, registration required)
- <http://medicine.iupui.edu/clinpharm/DDIs> (Flockhart DA, Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007))

List of references available on request. Date of preparation: January 2009

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics for specific information on a drug

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