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DRUG INTERACTIONS (2): FREQUENTLY ASKED QUESTIONS

- **Drug interactions with anticoagulants and/or antiplatelet agents can result in an increased risk of bleeding or thrombosis**
- **Co-administration of methotrexate with trimethoprim can result in myelosuppression and nephrotoxicity**
- **Co-administration of non-steroidal anti-inflammatory drugs with certain drugs including selective serotonin reuptake inhibitors is associated with an increased risk of gastrointestinal bleeding**
- **Drug interactions should always be considered for women using hormonal contraceptives**
- **Certain drug interactions can increase the risk of QT interval prolongation**
- **Tobacco smoking can reduce plasma levels of some drugs**

INTRODUCTION

As discussed in the previous bulletin, which outlines the principles of drug interactions, it is important to recognise the potential for a drug-drug interaction (DDI) in an individual patient and to take appropriate action to avoid harm. Potential DDIs should be evaluated based on the clinical risk and the benefit of the medicines. In addition to prescribed medicines, it is also important to consider over-the-counter medicines (e.g. non-steroidal anti-inflammatory drugs [NSAIDs], proton pump inhibitors [PPIs] and domperidone), which may contribute to a potential DDI. This second bulletin on drug interactions will deal with some frequently occurring questions relating to DDIs in clinical practice, for which the NMIC has provided practical guidance.

DRUG-DRUG INTERACTIONS AND ANTICOAGULANTS

Anticoagulants (such as warfarin and direct oral anticoagulants [DOACs], also known as non-vitamin K antagonist oral anticoagulants [NOACs]) are effective for the prevention and/or treatment of thrombosis for various conditions.[1,2] They have a narrow therapeutic index; DDIs involving anticoagulants are associated with an increased risk of bleeding or thrombosis, and hospitalisations.[3-5] The NMIC receives many enquiries relating to pharmacokinetic (PK) and pharmacodynamic (PD) DDIs involving anticoagulants.

Pharmacokinetic DDIs involving warfarin: Warfarin reduces the amount of vitamin K which activates clotting factors II, VII, IX and X.[3,6] **Warfarin is metabolised by the cytochrome P450 (CYP) isoenzymes CYP2C9, 1A2 and 3A4.**[6] It is a racemic mixture consisting of 2 isomers; with the S-isomer (mainly metabolised by CYP2C9) being up to 5 times more potent than the R-isomer (metabolised by CYP1A2 and CYP3A4).[3,6] **Many drugs are inhibitors or inducers of these isoenzymes (including drugs such as anti-infectives and cardiovascular drugs), resulting in potential PK DDIs when co-administered with warfarin**. Monitoring of the INR and dose adjustment of warfarin may be required when it is co-administered with a drug that is an inhibitor or inducer.[7] It is also important to note that stopping an interacting medicine can also cause an adverse effect.[7] For example, an increase in warfarin's anticoagulant effect can occur on stopping carbamazepine.[7] It is important to consider other factors that may contribute to the increase in risk of a clinically relevant DDI (e.g. acute illness, co-morbidities, age, diet, renal/hepatic impairment and polypharmacy).[3,6]

Consideration should also be given to concomitant drugs administered topically. For example, topical miconazole (including over-the-counter creams and oral gels), which is a CYP2C9 and CYP3A4 inhibitor may enhance the anticoagulant effect of warfarin.[8,9]

Management: Co-administration of topical miconazole with warfarin should be avoided; if this is not possible, the patient should be advised of an increased bleeding risk, the INR monitored and warfarin dose reduced if necessary.[3,8,10,11]

Pharmacokinetic DDIs involving DOACs: The DOACs currently authorised in Ireland include dabigatran (a direct thrombin inhibitor), rivaroxaban, apixaban and edoxaban (direct factor Xa inhibitors). **The DOACs are substrates for the efflux transporter P-glycoprotein (P-gp)**, therefore drugs that induce (e.g. carbamazepine, phenytoin, rifampicin) or inhibit (e.g. ciclosporin, dronedarone, erythromycin, ketoconazole) P-gp may affect DOAC plasma concentration, resulting in an increased risk of thrombosis or bleeding respectively.[2] **Factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) are substrates for CYP3A4**, therefore DDIs may occur when these drugs are co-administered with CYP3A4 inducers (e.g. rifampicin) or inhibitors (e.g. dronedarone, clarithromycin, fluconazole).[1,2] To reduce the risk of bleeding with concurrent inhibitors, either DOACs should be co-prescribed in a lower dosage (e.g. dabigatran, edoxaban) or the interacting drugs should be avoided altogether.[7] **There are PK differences between the various DOACs and factors such as a patient's age, weight and renal function can also impact on a clinically relevant DDI occurring**, therefore the individual Summary of Product Characteristics (SmPC) should be reviewed for full prescribing information.

An example of a PK drug interaction involving a DOAC is the co-administration of apixaban and clarithromycin. Clarithromycin is a strong inhibitor of CYP3A4 and a moderately potent inhibitor of P-gp which leads to a slightly increased exposure to apixaban.[12,13]

Management: Some sources recommend that no dose adjustment of apixaban is required when co-administered with clarithromycin, however the patient should be advised to be aware of an increased risk of bleeding;[12,13] other sources advise alternative antibiotic therapy.[13]

Pharmacodynamic DDIs involving anticoagulants: Patients on anticoagulants are at risk of potential PD DDIs when prescribed with other medications that can also increase the risk of bleeding (e.g. NSAIDs [see the section on NSAIDs to follow], antiplatelet drugs).[2,12,14-16] A further example of a PD DDI is the use of selective serotonin reuptake inhibitors (SSRIs) with anticoagulants. Serotonin released from platelets has an important role in regulating the haemostatic response to injury as it potentiates platelet aggregation. At therapeutic doses, SSRIs can block this reuptake of serotonin by platelets leading to serotonin depletion, impairment of haemostatic function and an increased risk of bleeding.[17] Risk factors for bleeding with SSRIs include age >65 years, previous history of GI bleed, history of stroke, peptic ulcer, hypertension, liver disease, renal disease, labile INR medication usage predisposing to bleeding, history of alcohol misuse and smoking.[18,20]

Management: There is a potential for a PD DDI in patients who are co-prescribed warfarin or a DOAC with a SSRI.[4,17-19] **Caution is advised when prescribing anticoagulants and SSRIs; patients should be advised of an increased risk of bleeding or prolonged bleeding** and to seek medical advice if this occurs.[12,14-16,19] Consider a PPI for gastroprotection when SSRIs are prescribed to a patient who is anticoagulated.[20]

DRUG-DRUG INTERACTION BETWEEN CLOPIDOGREL AND PROTON PUMP INHIBITORS

Clopidogrel is a thienopyridine antiplatelet drug prescribed with aspirin in acute coronary syndromes, including acute MI and unstable angina, and in coronary artery stenting. It is also used as an alternative to aspirin for the prophylaxis of thromboembolic events in patients with chronic occlusive peripheral arterial disease or other atherosclerotic conditions such as recent myocardial infarction (MI) or stroke.[21,22] Clopidogrel is metabolised to its active metabolite partly by CYP2C19 and all PPIs can inhibit this enzyme to varying degrees, therefore potentially inhibiting the metabolic activation of clopidogrel and decreasing its efficacy.[22,23] Evidence for a PK DDI between clopidogrel and PPIs is from several well-controlled studies; the data suggest that **the effect is greatest with high-dose omeprazole (80 mg daily), which slightly decreases exposure to the active metabolite of clopidogrel, and is smallest with pantoprazole which negligibly decreases its exposure.[19]** The Health Products Regulatory Authority (HPRA), the European Medicines Agency (EMA), the Medicines and Healthcare Regulatory Agency (MHRA) in the UK and the Food and Drug Administration (FDA) in the United States, as well as the SmPC for clopidogrel discourage use of the PPIs omeprazole and esomeprazole in patients taking clopidogrel.[22-24]

Management: There is insufficient evidence regarding which PPI is least likely to interact.[19,22] Based on data from PK/PD studies and the COGENT study, **pantoprazole is the least likely to interact and lansoprazole and rabeprazole are also suitable alternatives.[22]** Treatment decisions regarding concomitant use of clopidogrel and PPIs must balance the overall risks and benefits and consider the risk of cardiovascular and GI complications in individual patients. In some patients the benefits of a PPI may outweigh the risk of reduced clopidogrel efficacy.[19,22] The specialist interaction source, Stockley, also advises that it would seem reasonable to consider use of an alternative antiplatelet agent, free of interaction with PPIs, if their use is essential.[19]

DRUG-DRUG INTERACTIONS AND METHOTREXATE

Methotrexate, a folic acid antagonist, is an antineoplastic agent and immunosuppressant.[21,25] It is used for the treatment of inflammatory diseases and cancers and is available in both oral and injectable formulations.[26] Methotrexate, in very high doses (individual doses above 1 g/m^2) is used to treat some malignant diseases,[21] while low-dose methotrexate is used in the treatment of inflammatory diseases, such as rheumatoid arthritis and psoriasis.[26] Low–dose methotrexate (up to 25mg) should be administered once a week.[26,27] **Methotrexate is excreted primarily by the kidneys via glomerular filtration and active transport.[25]** Interaction with other drugs might affect renal, and possibly hepatic, clearance of methotrexate by inhibition of methotrexate transporter proteins;[19] this can lead to methotrexate toxicity which can be severe or life-threatening.[19]

Methotrexate and trimethoprim/ or co-trimoxazole (sulfamethoxazole with trimethoprim): There is an established DDI between methotrexate and trimethoprim/ co-trimoxazole; however the mechanism for this potential DDI is not fully understood.[19] Both methotrexate and trimethoprim can increase the risk of myelosuppression[9,28] and nephrotoxicity;[9] they can both suppress the activity of dihydrofolate reductase and may act additively to produce folate deficiency, which could lead to some of the bone marrow changes seen.[19] **Numerous cases of severe bone marrow depression (some of which were fatal) have been reported in patients given low-dose methotrexate and trimethoprim.[19]**

Management: Some sources advice against the combination,[13,19] including the HSE antibiotic prescribing website which recommends the use of an alternative antibiotic.[13] **If both drugs must be used, the haematological profile should be very closely monitored because the outcome can be life-threatening.[19]**

Methotrexate and penicillins: Penicillins can in individual cases reduce the renal clearance of methotrexate, resulting in increased serum concentrations of methotrexate with simultaneous haematological and GI toxicity.[28] Evidence for an interaction is limited to case reports, which indicate that serious interactions between methotrexate and penicillins are uncommon.[19] It is not known why only a few patients have been affected and what other factors might have contributed, but the problem does not seem to be confined to patients receiving high-dose methotrexate.[19]

Management: **If concurrent use of methotrexate and penicillin is required,** careful monitoring for signs and symptoms of methotrexate toxicity (i.e. haematological and gastrointestinal toxicity) is advised.[13,29]

Methotrexate and proton pump inhibitors (PPIs): The evidence for an interaction between methotrexate and PPIs is mostly from case reports and retrospective studies,[25] which suggest that concomitant use of methotrexate (particularly at high dosages) with PPIs (e.g. esomeprazole, omeprazole, pantoprazole) may decrease methotrexate clearance, resulting in elevated and prolonged serum concentrations of methotrexate and/or its metabolite hydroxymethotrexate and possibly leading to methotrexate toxicity.[25] There appears to be limited evidence of an interaction involving low doses of methotrexate with PPIs.[19] However, one case report involving pantoprazole and a 15mg weekly intramuscular dose of methotrexate, where a male patient developed severe generalised myalgia, introduces a note of caution in patients given low-dose methotrexate.[19]

Management: Caution or avoidance of high-dose methotrexate/PPI combination is advised.[9] The specialist interaction source, Stockley's Interactions Checker, advises that routine methotrexate monitoring should be adequate to detect any toxicity.[8]

Methotrexate and alcohol: Some inconclusive evidence suggests that the consumption of alcohol might increase the risk of methotrexate-induced hepatic cirrhosis and fibrosis.[19] There is a potential PD DDI as both methotrexate and alcohol can increase the risk of hepatotoxicity;[9] no direct causal relationship has been established.[19]

Management: Patients may drink alcohol whilst taking long-term low weekly doses of methotrexate (25mg or less) for skin conditions, rheumatoid arthritis and other inflammatory conditions, but **they should be advised that both alcohol and methotrexate can potentially damage the liver**, therefore they should not drink more alcohol than recommended by national guidelines.[27] The HSE provides weekly low-risk alcohol guidelines on its website.[30]

DRUG-DRUG INTERACTIONS AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs have analgesic and anti-inflammatory effects and are used for the treatment of continuous or regular pain associated with inflammation.[9] NSAIDs are commonly prescribed in primary and secondary care and are also available over-the-counter.[31,32] All NSAIDs inhibit platelet function and cause gastric erosions, resulting in an increased risk of GI bleeding.[33] Risk factors for NSAID-induced GI toxicity include age >65 years, high dose NSAIDs, prolonged administration of NSAIDs, co-administration of other drugs that increase the risk of GI adverse effects, serious co-morbidity, alcohol misuse and heavy smoking.[9]

NSAIDs and anticoagulants used in combination result in a potential PD DDI. Evidence suggests that combined use of NSAIDs and coumarin anticoagulants or DOACs increases the risk of GI haemorrhage, which is higher than that seen with either drug used alone.[19] DDIs involving NSAIDs and anticoagulants are a cause of hospitalisations due to GI bleeding.[34,35] Another consideration for use of NSAIDs in a patient on anticoagulants is the risk of cardiovascular events. All NSAIDs (including cyclo-oxygenase-2 selective inhibitors) are, to varying degrees, associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those receiving high doses long term.[9]

Management: It is recommended to avoid the concomitant use of NSAIDs and anticoagulants if simple analgesics can be used instead. If concurrent use is necessary be aware of the potential risks of bleeding and consider gastroprotection (such as a PPI).[8] If any NSAID is used with an oral anticoagulant, the patient should be advised of an increased bleeding risk and the INR monitored for those on warfarin.[33]

NSAIDs and methotrexate: Increased methotrexate toxicity, sometimes life-threatening, has been seen in a few patients also taking NSAIDs, whereas other patients have taken an NSAID and methotrexate uneventfully. The development of toxicity might be dose-related and the risk appears to be lowest in patients taking low-dose methotrexate for psoriasis or rheumatoid arthritis who have normal renal function.[8] The mechanism of interaction is complex and perhaps multifactorial.[8] NSAIDs can reduce renal elimination of methotrexate, leading to toxicity.[36]

Management: In general, concurrent methotrexate and NSAIDs need not be completely avoided, but in particular, **patients receiving low-dose methotrexate should be advised to avoid self-medication with over-the-counter NSAIDs such as aspirin or ibuprofen.** For high-dose methotrexate, monitoring of methotrexate concentrations post-dose is routine and will identify any decreases in elimination which should be managed accordingly.[19]

NSAIDs and corticosteroids used in combination can result in a potential PD DDI. Corticosteroids or NSAIDs alone may be risk factors for GI bleeding and ulceration.[19] **The concurrent use of NSAIDs and corticosteroids increases the risk of GI bleeding and probably ulceration.[19]** There may also be a potential PK DDI with NSAIDs displacing both administered and endogenous corticosteroids from their plasma protein binding sites.[19] While the majority of these PK DDIs seem unlikely to be of clinical significance, they may well contribute to the adverse effects of both drugs, particularly the corticosteroids.[19]

Management: Prescribers should be aware of the increased risk of GI bleeding, when co-administering NSAIDs and corticosteroids; it may be prudent to consider the use of gastroprotection, especially in those aged >65 years.[9]

NSAIDs and selective serotonin reuptake inhibitors (SSRIs) used in combination result in a potential PD DDI. As described in a previous section SSRIs are associated with an increased risk of bleeding.[19] A large number of studies have found that SSRIs alone increase the risk of GI bleeding, mainly from the upper GI.[19] **Co-prescription of low-dose aspirin at least doubles the risk of GI bleeding associated with SSRIs alone, and co-prescription of NSAIDs approximately quadruples the risk.[37]**

Management: Alternatives such as paracetamol or less gastrotoxic NSAIDs, such as ibuprofen, should be considered with concurrent SSRIs. If the combination of an SSRI and an NSAID cannot be avoided, prescribing of gastroprotective drugs, such as PPIs, should be considered, especially in elderly patients, who seem to be at greater risk of SSRI-associated bleeding, and in those with a history of GI bleeding.[19]

DRUG-DRUG INTERACTIONS WITH CONTRACEPTIVE AGENTS

DDIs should always be considered for women that are taking concomitant medication with hormonal contraceptives (other than intrauterine contraception or depot medroxyprogesterone acetate [DMPA], both of which are not affected by any drug interactions).[38] Plasma levels of contraceptive hormones may be altered by concurrent use of other medication and hormonal contraceptives may themselves alter plasma levels of concurrent medication.[38] Clinically significant PK DDI examples of each are as follows:

Enzyme-inducing drugs and combined hormonal contraception (CHC): CHC includes combined oral, transdermal and vaginal ring contraceptive agents. Enzyme inducers include rifampicin, carbamazepine, phenytoin, modafinil and St John's wort; these interacting drugs can reduce the efficacy of CHCs by induction of liver enzymes, which leads to increased elimination of both oestrogen and progestogen.[38,39] This clinically significant effect can halve blood levels of CHCs and be maintained for 28 days after stopping the enzyme-inducing drug.[39] Recent reports suggest widespread use of the enzyme inducer modafinil as a 'smart drug' to enhance cognitive function during exam periods.[38] Women known to be taking modafinil off-licence should be warned about the potential impact on contraceptive efficacy.[38]

Management: Women starting any enzyme-inducing drugs should be advised of the potential interaction with hormonal contraception and be offered a reliable method unaffected by enzyme-inducers.[38]

Lamotrigine and combined hormonal contraception: Women with epilepsy who are taking lamotrigine monotherapy and CHC are at risk of an iatrogenic seizure.[39] **Lamotrigine levels can be lowered by CHCs** because of induction by ethinylestradiol (EE) of the enzyme glucuronyltransferase which eliminates lamotrigine through glucuronidation.[39]

Management: As this drug interaction is clinically significant, switching to any non-EE-containing contraceptive is preferable.[38,39]

DRUG-DRUG INTERACTIONS AND THE QT INTERVAL

If the QT interval on the ECG becomes excessively prolonged, ventricular arrhythmias can develop, in particular a type of polymorphic tachycardia known as torsade de pointes (TdP).[19] **DDIs can increase the risk of QT interval prolongation in a number of ways:** (1) PD DDI: the concurrent use of more than one drug that prolongs the QT interval, (2) PK DDI: the metabolism of a drug which can prolong the QT interval is inhibited by another drug and (3) Electrolyte disturbance: drugs that have an effect on electrolytes can interact with QT-prolonging drugs (e.g. methadone, amiodarone, citalopram, macrolide antibiotics) because electrolyte disturbance can increase the risk of QT prolongation e.g. diuretics by causing hypokalaemia.[40] Of note there are also individual risk factors that can increase the risk of drug-induced QT prolongation e.g. age over 65 years, female gender (for further information see our bulletin NMIC 2015, Volume 21, No.6).[41,42]

An example of a potential DDI affecting QT prolongation is the combination of domperidone (available over-the-counter) and clarithromycin. Domperidone, a substrate for CYP3A4, is contraindicated during co-administration with QT-prolonging drugs and also with potent CYP3A4 inhibitors (regardless of their QT-prolonging effects).[43,44] Clarithromycin is a potent CYP3A4 inhibitor and is predicted to increase the exposure to domperidone (PK DDI).[8,19] The specialist QT website, CredibleMeds, includes both clarithromycin and domperidone on its list of Drugs with known TdP risk (PD DDI).[45]

Management: **The concomitant administration of domperidone and clarithromycin is contraindicated.**[43,46]

DRUG INTERACTIONS AND TOBACCO SMOKING

Polycyclic aromatic hydrocarbons found in tobacco smoke increase the metabolism of some drugs by inducing hepatic enzymes.[9] Of the tobacco-induced isoenzymes, CYP1A2 is the most clinically significant as many drugs are substrates for this enzyme.[47] **Tobacco smoking can therefore reduce plasma levels of some drugs, with patients requiring higher doses;[9] consequently these doses may need to be reduced if someone stops smoking.** Even if the degree of enzyme induction is weak, it can still produce clinically significant events for drugs with a narrow therapeutic index; patients taking drugs with a narrow therapeutic index should be monitored closely when any lifestyle modification is made.[47] A person's smoking status is important to consider also, for example if admitted to an inpatient setting, both in assessing the requirement for nicotine replacement therapy (NRT) and also to determine whether a change in smoking status might potentially result in a drug interaction. **The SmPC can be consulted when assessing the likelihood of interactions between a specific drug and tobacco smoking**; it is a useful source of information to identify the enzymes involved in a drug's metabolism.

Although most interactions between drugs and tobacco smoking are not clinically significant, **it is important to be aware of a small number of drugs which may require dose adjustment or increased monitoring when smoking status is altered.**[47] Some examples of these drugs include, but are not limited to, aminophylline, theophylline, clozapine and erlotinib.[8,47] It is recommended that if the affected drug is prescribed under the supervision of a specialist, their input should be sought if the patient changes their smoking status.[47]

For example, clozapine is almost completely metabolised by CYP1A2 and 3A4, and to some extent by 2C19 and 2D6.[48] Smokers may need higher doses due to increased clearance of clozapine;[8,47] smoking may reduce plasma clozapine levels by 50%, with a greater reduction possible in those also taking valproate.[20] **There have been case reports of adverse effects in patients on clozapine who abruptly stopped smoking.**[47]

Management: Monitoring of plasma levels and dose reduction is suggested if a patient on clozapine stops smoking;[20,47] a requirement for increased doses should be anticipated in the event of smoking relapse.[47]

List of references available on ePublication on www.nmic.ie. Date of publication: November 2020