Medicines Safety Matters

Newsletter for Prescribers & Community Pharmacists

Health and Social Care Board

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Reducing the risk of methotrexate toxicity

Using higher strength folic acid

Oral methotrexate is widely prescribed for many indications e.g. rheumatoid arthritis, psoriatic arthritis. For all indications, it is important that it is co-prescribed with folic acid.

Why?
Folic acid reduces the risk of gastrointestinal and haematological toxicity associated with methotrexate. The usual dose is one 5mg tablet once a week taken one to two days **after** the methotrexate dose. (Note: 5mg folic acid is also used when planning a pregnancy or during pregnancy by women taking anti-epileptic medicines).

What happened?
A patient was prescribed and received 400mcg instead of the 5mg strength. The dose of folic acid was not enough to counteract the toxic side effects of the methotrexate and the patient developed pancytopenia requiring hospital treatment. The error occurred when the incorrect folic acid strength was selected by the prescriber from the drop down drug list.

Folic acid 5mg once a week, taken one or two days after methotrexate

Learning points:

For prescribers:

- Ensure that folic acid is always co-prescribed with methotrexate, the correct dose is folic acid 5mg.

For community pharmacists:

- The prescription must be clinically checked prior to dispensing
- Query any prescriptions for the 400mcg strength of folic acid that have been prescribed in conjunction with methotrexate directly with the prescriber.

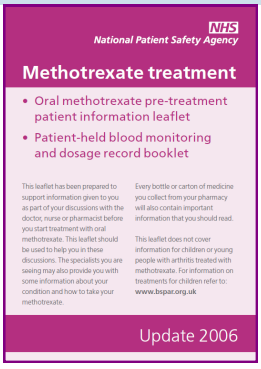
The patient knows best!

In Medicines Safety Matters November 2014, we highlighted incidents involving the serious interaction between **methotrexate** and **trimethoprim** or **co-trimoxazole** (Septrin®). This is a potentially **lethal** interaction and the combination is contraindicated both for **all** doses of methotrexate and for even **short** courses of the antibiotics.

In some of the reported incidents it was the **patient** who recognised that they should not have been prescribed trimethoprim rather than the GP or the pharmacist. The patients did not take their trimethoprim, reported their concerns and the antibiotic was changed.

These cases show the importance and the benefits of ensuring that patients are well informed about their methotrexate therapy through counselling and patient information.

In Northern Ireland it is recommended that all patients receive the NPSA Methotrexate booklet which highlights this dangerous interaction.



"You must not take co-trimoxazole (Septrin®) or trimethoprim whilst taking methotrexate. These can react with methotrexate and be dangerous."

For further information on recommendations for the safe use of methotrexate, a GP practice audit and how to order booklets: www.medicinesgovernance.hscni.net/primary-care/high-risk-medicines/

Oral miconazole & warfarin interaction

A 73 year old patient who was taking warfarin presented to their GP with bleeding gums and flank pain. Their INR was >8 and the patient attended hospital where they received IV vitamin K.
A review of what may have caused the high INR revealed that the patient had obtained oral miconazole gel (Daktarin Oral Gel®) 2 weeks previously from their pharmacy for the treatment of oral candidiasis.

What is the interaction?
Miconazole is a **potent inhibitor** of warfarin metabolism and reports of bleeding and raised INRs are well documented for this interaction.
Vaginal and topical administration of miconazole can also affect warfarin but the oral route usually has a more profound effect because the gel is swallowed after use in the mouth.

Advice for prescribers & pharmacists:

If you are considering prescribing or supplying miconazole, check first if the patient is on warfarin.

Miconazole oral gel should generally be avoided in patients taking warfarin.
If it cannot be avoided, the INR should be monitored and signs of bleeding should be followed up.

Soya & nut allergy

A patient with a known nut allergy took Toviaz® (fesoterodine fumarate) for a number of weeks and unfortunately suffered a severe anaphylactic reaction.
Toviaz® contains soy-bean oil in the tablet coating and is therefore contraindicated in patients with peanut or soya allergy.
There are significant numbers of medicines available (both over-the-counter and on prescription) that are contraindicated in patients with a peanut allergy.
As with all medicinal products that are contraindicated in specific patient groups, alternative products may be prescribed to meet individual patient need.

Always check the individual product SPC or patient information leaflet when prescribing/supplying new medicines to a patient with peanut or soya allergy

Each medicine's SPC will provide full details of product ingredients and potential allergens
www.medicines.org.uk

If in doubt, contact the pharmaceutical company

When to measure lithium levels

Recent audit results have highlighted some issues regarding lithium monitoring. Lithium monitoring should be undertaken every 3 months and blood tests need to be taken **12 hours*** after the last lithium dose and at the same time of day in order to obtain the most reliable result. Most patients take their lithium once daily 'at night' so this works out quite well. For patients on a twice daily dose, morning and night, the morning dose should be omitted on the day of the blood test.

Why is the timing important?
A blood test taken too early, before 12 hours has elapsed, would result in over-estimating the actual lithium level and potentially lead to lithium being unnecessarily stopped or the dose decreased - risking a relapse. Conversely, if the test is taken late after the 12 hour period, the lithium level would be under- estimated possibly leading to a dose increase and potential lithium toxicity.

*One-two hours' flexibility is generally acceptable however beyond this will depend on the individual case.

Highlight the importance of timing when arranging blood tests for patients on lithium

If BD regimen, omit the morning lithium dose on the day of the test

Aim for a sample time 12 hours after the last dose

For further information on the primary care lithium audit and results refer to the HSCB Primary Care Intranet:
http://primarycare.hscni.net/PharmMM_Clinical%20Resources_Lithium.htm

'Gliflozins': Remember to Monitor Renal Function

What are the 'gliflozins'?
Sodium–glucose co-transporter 2 (SGLT2) inhibitors ("gliflozins") are a **new class of drugs** used to improve glycaemic control in adults with type 2 diabetes (Table 1). They block the reabsorption of glucose in the kidneys and promote excretion of excess glucose in the urine producing an osmotic diuresis, which may reduce intravascular volume and decrease blood pressure. Over 11,200 prescriptions for these products have been dispensed in N.I. during the first six months of 2015.

Who is at risk?
For patients with renal impairment there is:

- Increased adverse reactions associated with volume depletion (e.g. postural dizziness, hypotension)
- Reduced (and possibly absent) efficacy of the gliflozins due to the renal impairment.

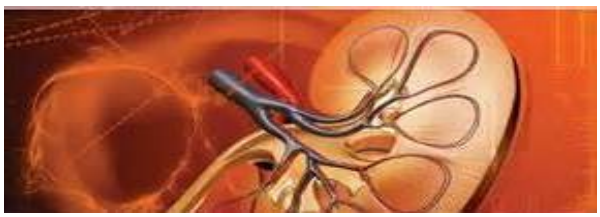
Be aware of the risks of hypovolaemia (due to osmotic diuresis) in:

- Patients with CVD
- Patients taking anti-hypertensive therapy with a history of hypotension or diuretics
- Elderly patients
- Inter-current conditions that may lead to volume depletion (such as a GI illness)

What is the issue?
Patients have been identified at hospital diabetic review who were incorrectly taking gliflozins in the presence of renal impairment (see Table 2).

Table 1: Gliflozin Medicines

Drug name	Brand name	Brand including metformin
Canagliflozin	Invokana▼	Vokanamet▼
Dapagliflozin	Forxiga▼	Xigduo▼
Empagliflozin	Jardiance▼	Synjardy ▼



How often should I monitor renal function?

- Prior to initiation and then at least annually
- Prior to initiation of any concomitant drug that may have a negative impact on renal function
- During inter-current conditions that may lead to volume depletion (e.g. GI illness)
- When renal function is approaching level requiring cessation of gliflozin, at least 2-4 times per year

Table 2

Renal Function eGFR <60mL/min/1.73 m^2 or CrCl mL/min	Canagliflozin	Dapagliflozin	Empagliflozin
< 60 ml/min at initiation	Do not use	Do not use	Do not use
<60 ml/min during treatment	If tolerated, reduce to/ maintain at licensed starting dose	Stop	If tolerated, reduce to/ maintain at licensed starting dose
<45 ml/min during treatment	Stop	Stop	Stop

Advice for Prescribers

- Monitor renal function before initiation and at least annually thereafter
- Advise patients to report symptoms of volume depletion
- For patients who develop volume depletion, monitor volume status and consider temporary interruption of treatment with gliflozin until the condition is corrected
- Remember: these drugs have also been associated with diabetic ketoacidosis

Advice for Community Pharmacists

- Remind patients of importance of attending GP practice for routine blood tests
- Remind patients to report symptoms of dehydration (e.g. postural hypotension, dizziness, feeling very thirsty, very weak or tired, passing little or no urine, fast heartbeat) to their GP

References
SPC and PIL www.medicines.org.uk (accessed 11th September 2015)
SGLT2 inhibitors:risk of diabetic ketoacidosis (Drug Safety Update, MHRA, June 2015)

Lost in transcription - hospital letter to HS21

Examples of recent prescribing errors due to incorrect transcribing from hospital letters are listed in Table 3. In some cases, the incorrect medication was prescribed for several months before the error was identified.

The risk of error is **higher** when transcribing than in decision-making tasks such as prescribing.

Seven of the examples listed in Table 3 resulted in patient harm.

Contributory factors identified in these incidents are listed below along with advice for actions that can reduce the risk of errors.

Examples of Transcribing Errors in Primary Care

Table 3

Intended by hospital	Prescribed in primary care
Advagraf 5mg	Advagraf 500mcg
Folic acid 5mg (patient on methotrexate)	Folic acid 400mcg
Oxybutynin 5mg/5ml (child)	Oxynorm 5mg/5ml
Captopril 5mg/ml (child)	Captopril 5mg/5ml
Ethinylestradiol 2 microgram (12 year old)	Ethinylestradiol 2mg
Gabapentin 600mg tds	Pregabalin 600mg tds
Rivaroxaban 15mg bd for 21 days then 20mg daily	Rivaroxaban 15mg bd no dose reduction
Methylphenidate 160mg	Methylphenidate 340mg
Nutrison Multi-fibre Energy	Nutrison Multi-fibre (500kcal & 20g protein less per day)

Contributory factors

Inadequate check on medication dose and/or appropriateness

Incorrect selection from clinical drug dictionary

Similar drug names

Unclear directions on outpatient/hospital letter

Prescriber unfamiliar with drug regime

Medication review did not include a check of dose and patient response

Insufficient patient counselling i.e. intended medication/dose and response

Prescription queries were not checked directly with the prescriber.

Actions that reduce risk

Set aside protected time for making changes from hospital/outpatient letters

Ensure the correct medication and strength is selected from the computer list

Double check all transcribed medication to ensure it is correct

Check unclear medication changes/requests with the consultant team

Check medication dose and patient response/ side-effects as part of medication reviews

The patient often knows their medication best and can be part of the safety chain if their medication is explained to them

Pharmacists should carry out a clinical check of all prescriptions and speak directly to a prescriber regarding clinical queries