

This edition contains articles on:

- Voriconazole: prescribing safely
- Corticosteroids in palliative care
- ADTC decisions summary and new guidelines
- Webwatch: drugs in lactation
- Prescribing and addiction issues in prisons

Voriconazole: prescribing safely

Voriconazole is a broad spectrum, triazole antifungal agent indicated primarily in immunocompromised patients with progressive, possibly life-threatening infections, eg invasive aspergillosis. Treatment of candidaemia in non-neutropenic patients is restricted to those who cannot tolerate or are at increased risk of side effects of amphotericin B. The NHSGGC Formulary restricts its use to specialist prescribers only.

Voriconazole interacts with a variety of drugs due to inhibition of cytochrome P450 enzyme system. Prescribers will be aware of the importance of considering the potential for interactions when they prescribing new treatments. For more information on drug interactions and cytochrome P450, please refer to [PostScript Acute 11 \(June 2013\)](#) and [2 \(January 2011\)](#).

Examples of Significant Interactions

Voriconazole has several associated interactions, many of which are clinically significant. Always check with the SPC, BNF or other information source and if the combination is contraindicated do not co-prescribe.

Examples of drugs that should be avoided with voriconazole include carbamazepine, efavirenz, ergotamine, everolimus, pimozide, quinidine, rifampicin, ritonavir, sirolimus and St John's Wort.

Examples of drugs that require additional monitoring with voriconazole include immunosuppressants (ciclosporin, tacrolimus), warfarin and coumarins, opioid analgesics, benzodiazepines, NSAIDS, statins, omeprazole, sulphonylureas. Check the SPC for details of monitoring required.

QT interval prolongation

As well as being an enzyme inhibitor, voriconazole has been associated with QT interval prolongation.

There have been rare cases of torsades de pointes in patients on voriconazole who had risk factors. More information on drug induced QT interval prolongation can be found [here](#).

Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, such as

- congenital or acquired QT-prolongation
- cardiomyopathy, in particular when heart failure is present
- sinus bradycardia (<50 bpm)
- existing symptomatic arrhythmias
- concomitant medicinal product that is known to prolong QT interval
- history of cardiotoxic chemotherapy
- uncorrected hypokalaemia, hypocalcaemia or hypomagnesaemia

Hepatic toxicity

In clinical trials, there have been rare cases of serious hepatic reactions including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. Hepatic reactions occurred primarily in patients with serious underlying medical conditions; predominantly haematological malignancy. Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy.

Monitoring of hepatic function

Patients receiving voriconazole must be carefully monitored for hepatic toxicity. Clinical management should include laboratory evaluation of hepatic function (specifically ALT and AST) at the initiation of treatment with voriconazole and at least weekly for the first month of treatment. If the liver function tests become markedly elevated, voriconazole should be discontinued, unless the medical judgment of the risk-benefit of the treatment for the patient justifies continued use. Monitoring will be carried out by the specialist who recommended treatment. There is no shared care protocol in place.

Key points

- It is essential that healthcare professionals who prescribe take responsibility for identifying and acting on drug interactions to minimise the risk to patients. Ensure effective medicines reconciliation.

- Prescribers must take responsibility to ensure the medication can be prescribed safely. The dispensing pharmacist cannot always check interactions as they may not have information on the patient's full medical history or other prescribed drugs. Drugs prescribed in hospital are unlikely to be on ECS. Interaction checks are not automatic via electronic systems.
- Voriconazole is restricted to specialist use and should only be prescribed for indications listed in the NHS GGC Formulary.
- Always check for interactions with all existing therapy before voriconazole is started. If the combination is contraindicated, do not co-prescribe.
- If there is an interaction, decide on a management plan and document the details of the interaction in the patient's medical notes. Consider what options exist for changing one or other of the drugs to allow safe prescribing. Consultation with the relevant specialists may be required.
- Ensure the plan is documented, followed and communicated to other members of the multidisciplinary healthcare team including hospital and community pharmacies and the patient's GP.
- Interactions must be considered when prescribing any new medication
- If unsure how to manage an interaction or of the potential significance of an interaction, contact pharmacy for advice.
- GPs should consider adding voriconazole as an "outside" medication on repeat prescribing lists given the potential for interactions.

Sources to Check for Drug Interactions

- [BNF](#) Appendix 1
- The [Summary of Product Characteristics](#) (SPC)
- Clinical pharmacists, antimicrobial pharmacists, Medicines Information Service.

Corticosteroids in Palliative Care

Prompted by regular requests for advice about use of steroids in palliative care patients in the community, an audit was undertaken to establish the care issues and whether there were any problems. Notes from 15 community based patients were reviewed and the results were used to help inform guidance for improving the safety of prescribing.

One third of patient had treatment started by their GPs, with the rest initiated by a hospital doctor. Appetite stimulation was the main indication, although it wasn't always clear what the indication was. Most patients had a care plan in place and most were also prescribed PPIs.

At least 7 patients had at least 1 recognised side effect of their steroids: 4 had thrush, 3 had myopathy and 1 had insomnia. Only 3 of 15 were documented as having no side effects.

Safe and effective prescribing

Corticosteroids are often used in palliative care with many indications being for off-label uses. Good quality evidence (and consensus) for optimum dose and duration of treatment for each indication is lacking. However, there is general agreement that the minimum dose required to control symptoms (for the minimum time) is a sensible approach. Alternatives should be considered first and there should be a clear aim and plan of steroid treatment agreed with those involved in ongoing care of the patient. This should be clearly documented. In view of the potential for serious side effects, it is prescription and administration of steroids must be carefully monitored and frequently reviewed.

Indications

Traditionally steroids have been used as a 'tonic' to increase wellbeing and improve appetite. They have also been given where it is desirable to reduce inflammation or oedema or to 'buy time' in emergency situations until specific treatment can be administered or have time to work. In the palliative care setting, dexamethasone is the preferred steroid due to its reduced tablet burden and lower likelihood for fluid retention (reduced mineralocorticoid effect).

Potential side effects

Side effects are more likely (but not exclusively) with high doses or prolonged duration of treatment. **All** patients should be given a **steroid warning card** if expected to take corticosteroids for **≥3 weeks**.

| Side effect | Action to limit effect |
|---|--|
| Elevated blood glucose level | Consider monitoring weekly. Anti-diabetic medication may need reviewed. |
| Insomnia | Try to give as single morning dose. If dose needs to be split, aim to give second dose no later than 2pm but ideally before noon. |
| Agitation / psychiatric disturbance | Reduce dose or may need to stop. May need psychiatric advice. |
| Susceptibility to infection (especially thrush) | Monitor and treat if required. Steroids may mask signs of systemic infection. May need to increase steroid dose temporarily during infection due to inadequate stress response as a result of adrenal suppression. |
| Dyspepsia, peptic ulceration or perforation | Consider co-administration of PPI for gastric mucosa protection especially if dyspepsia develops or at risk, eg elderly, taking NSAIDs, |

| | |
|--------------|---|
| | previous peptic ulcer, likely high dose steroid or for long duration. |
| Osteoporosis | Consider prophylaxis if long term (>3-6months) treatment likely. Be mindful of polypharmacy issues. |

The risk of these and other side effects such as fluid retention, proximal myopathy (difficulty climbing stairs or rising from seat), avascular necrosis and typical Cushingoid effects can be reduced by using the smallest dose for shortest time possible.

Anecdotally, switching steroids may also help for some side effects, eg switching dexamethasone to prednisolone (<30mg) may help if proximal myopathy.

Drug interactions

Patients may need increased steroid dose if they are also taking drugs known to cause enzyme induction, eg phenytoin, carbamazepine, phenobarbital. Prescribers should also consider the effect of discontinuing steroids as the doses of some medications, eg warfarin, hypoglycaemics or insulin may need to be altered.

Regular review

If there is no benefit after 5-7 days, stop treatment. Steroids can be stopped abruptly if:

- given for less than 3 weeks (including recent previous courses),
- at a dose of less than 40mg prednisolone or equivalent,
- the patient has not received prolonged course of steroids in the last year,
- there is no other reason for adrenal suppression.

If patient is benefitting from steroid therapy, it may be possible to reduce the dose after one week (dependent on patient and symptoms) especially if they are receiving high doses. If symptom control deteriorates following dose reduction, it may be necessary to consider increasing to the previous dose. Thereafter a slower reduction may be possible.

If patient becomes unable to swallow (including at end of life), consider benefits and burdens of treatment and consider stopping or switching to subcutaneous administration.

New NHSGGC guidelines

The following guidelines have been added to the repository on Staffnet

- [Management of Cholesterol Levels Primary and Secondary Prevention of CHD and Stroke](#)

ADTC decisions summary

See the [website](#) for full list of medicines and details of indications and restrictions.

The following medicine was added to the Adult Formulary:

- **Levonorgestrel (Upostelle®)** for emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method is included in the Preferred List.

The following medicine was not added to the Formulary:

- **Fentanyl citrate buccal film (Breakyl®)** for the treatment of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain

The following medicine was added to the Paediatric Formulary

- **Tocilizumab IV infusion (RoActemra®)**, in combination with methotrexate (MTX) for the treatment of juvenile idiopathic polyarthritis in patients 2 years of age and older. Restricted to specialist use only.

Webwatch: Drugs in Lactation

The UK Drugs in Lactation Advisory Service (UKDILAS), was established as a national service in 1980 and is aimed mainly at supporting local medicines information services on all medicines-related aspects of lactation, but is also available to all health care professionals in the NHS, as well as to breastfeeding support organisations.

A new web-based resource has been launched which provides a risk-based assessment of all drugs currently used in the NHS and included in the BNF. It can be found at <http://www.midlandsmedicines.nhs.uk/content.asp?section=6&subsection=17&pageIdx=1>.

The database stratifies risk according to the evidence of known and possible risks to a breastfeeding infant when administering a medicine to the mother. It also advises, where possible, on alternative medicines which have a lower and more acceptable risk rating and provides a link to an evidence source.

Prescribing and addiction issues in prisons

Dr Grace Campbell, Lead Clinician in Prison Health highlights some recurring issues which face doctors in that setting.

Healthcare within prisons was a non-NHS service organised by the Scottish Prison Service until late 2011 when it became an NHS responsibility. Within NHSGGC boundaries there are currently three prisons; Greenock holds 255 prisoners, Lowmoss has 780 and Barlinnie has a population of around 1,300. There is high psychiatric morbidity, including addiction issues, within the prison population.

Case Study

A 35 year old man was admitted to a local prison on the following medicines:

- tramadol 50mg 1-2 capsules 6 hourly,
- gabapentin 600mg three times daily
- zopiclone 7.5mg at night
- methadone 1mg/mL

A urine test was positive for methadone, opiates and benzodiazepines. The patient stated the gabapentin and tramadol were for a fractured clavicle 12 months ago, and nerve damage to his hand. The prescribed dose of methadone wasn't clear, and as this was supplied from the Community Addiction Team and not the patient's GP, it was not included on the Emergency Care Summary. The patient was given a dihydrocodeine based detoxification until the methadone history was confirmed by the prescriber. He was also prescribed diazepam detoxification due to zopiclone and diazepam misuse.

The patient was given a supply of 56 tramadol 50mg capsules and 30 gabapentin 600mg tablets. On a routine medicines check the next day, he only had 12 tramadol capsules and 10 gabapentin tablets.

He was assessed by the prison's on duty GP and a pain assessment completed which found no clinical evidence of neuropathic pain or of severe pain meriting tramadol. Tramadol and gabapentin were discontinued and replaced with ibuprofen which was the treatment prescribed when the patient was liberated. Eight weeks later, the patient was readmitted on remand. Despite the changes made to his medication during the stay in prison he was now back on tramadol, gabapentin and zopiclone; all confirmed by the emergency care summary.

Learning Points

- Clear communication is vital when patients move from one care setting to another. This is as true for patients moving from prison to the community as it is for patient moving from hospital to community care.
- Drugs such as tramadol and zopiclone are addictive. They are like currency in a secure environment and, most likely, in the community.
- Gabapentin and pregabalin are also addictive and can potentiate opiate effects. There is strong evidence that they are subject to diversion, substitution and misuse amongst certain populations, particularly those in a secure environment.
- Implementing any changes to medicines can be challenging and may result in difficult consultations, verbal and physical abuse of staff, a high level of complaints and pressure on the community GP to reinstate.
- GPs receive NHS discharge summaries from the prison service with details of prescribed. Prison doctors can confirm any details for GPs concerned about re-prescribing problematic medication, or feeling under pressure to do so.
- The likely reclassification of tramadol to become a schedule 3 CD has prompted identification of all patients prescribed this drug in a secure setting. All patients will be individually assessed using the Pain Assessment Tool and transferred to another medication.
- Assessment of pain within substance misusing populations can be challenging. The prison pain assessment tool and algorithm can be shared with GPs on request.



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