Information for Health Care Professionals

Clozapine Toxicity and Therapeutic Drug Monitoring

Clozapine (Clozaril®) is an atypical antipsychotic medication indicated for treatment resistant schizophrenia (TRS). Although often a highly effective treatment its use is restricted due to the potential for severe and potentially life threatening adverse effects. This information sheet provides an overview of signs and symptoms of clozapine toxicity and outlines when to consider therapeutic drug monitoring. There should be psychiatric involvement in any patient admitted to hospital and on clozapine, with referral to the Consultation Liaison Psychiatry within 24 hours. Clozapine orders need to be reviewed and co-signed by Liaison Psychiatry.

Recognising the signs of clozapine toxicity

Clozapine toxicity can occur when clozapine levels are high and when there are sudden and large increases in clozapine levels.

It may be recognised by the following signs:	Toxicity can cause:
> Excessive sedation	> Seizures
> Confusion	> QTc prolongation
> Delirium	> Cardiac arrhythmia
> Hypersalivation	> Respiratory depression
> Myoclonus	> Sudden Cardiac Death

What causes clozapine toxicity?

Clozapine toxicity can be secondary to a number of factors:

- Intentional or unintentional overdose
- Concurrent prescription of interacting medications
- Changes in tobacco smoking
- Changes in doses
- Concurrent infection or inflammation

Therapeutic Drug Monitoring (TDM)

Clozapine levels are routinely recommended at least 6 monthly during maintenance therapy.

In addition, they should be measured on admission to hospital and when non-compliance is suspected.

The recommended therapeutic range is 350-600 µg/L, however some patients require higher levels; up to a maximum of 1000 µg/L. Levels should be measured 12-hours after the last dose, as the range is based on a 12-hour trough.

It can take up to a week for clozapine levels to be reported. If there is a suspicion of clozapine toxicity, clozapine can be held whilst the Psychiatric Liaison service is consulted.

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Drug interactions

Clozapine is primarily cleared hepatically by CYP1A2, and to a lesser extent by CYP3A4 and CYP2D6.

There are a number of clinically significant drug interactions that prescribers should be aware of (see Box 1).

Addition of strong CYP1A2 inhibitors should be avoided and if required, may necessitate pre-emptive dose reduction of clozapine.

Concurrent infection and inflammation

Evidence suggests that infection and inflammation can inhibit cytochrome P450 enzymes resulting in a significantly elevated serum clozapine concentration.

If an infection is present (e.g. pneumonia, UTIs, abscess), assess for signs of clozapine toxicity and if indicated perform clozapine TDM. Psychiatry involvement in dose changes is crucial.

Note: due to potential delay in reporting of clozapine levels pre-emptive dose reduction may be required based on presentation.

Changes in tobacco smoking

Smoking tobacco is a strong inducer of CYP1A2 and of clozapine metabolism.

Changes in tobacco smoking, i.e. due to intentional cessation or during hospitalisation can have a large effect on clozapine concentrations. This effect can appear within the 3-5 days and tends to be more apparent when smoking is reduced to less than 10 cigarettes per day.

When there is a significant change in smoking, patient awareness and close monitoring for signs of toxicity is important, with clozapine levels taken at day 1, 7, then weekly until stable. Pre-emptive reduction isn't routine.

Contact Psychiatry Liaison for advice in smoking cessation.

Dose changes

Dose changes can result in disproportionate changes in clozapine levels. Clozapine TDM is recommended 5-7 days after a dose change is made.

Re-titrating

The dose may need to be re-titrated to previous levels post resolution (i.e. post infection or after ceasing interacting medication).

Dose changes should be no more than 100mg every 5-7 days. Clozapine can only be re-initiated or re-titrated by Consultation Liaison Psychiatry.

It must not be recommenced at the previous prescribed dose if there has been a break of more than 48 hours.

Box 1: Drug interactions

This list is not exhaustive, and pharmacist or psychiatry advice on management is required.

Potential to Increase Clozapine Levels (enzyme inhibitors)	> Selective serotonin reuptake inhibitor (SSRIs) e.g. fluvoxamine (very large effect), fluoxetine, paroxetine, sertraline (large doses) > Caffeine (3-4 cups/ day, especially in non- smokers) > Some antibiotics such as quinolones i.e. ciprofloxacin (large effect), macrolides (erythromycin) > Oral contraceptives > Ritonavir
Potential to Depress Respiration	> Benzodiazepines (especially large parenteral doses or at start of therapy)
Potential for Anticholinergic Side Effects (e.g. constipation, urinary retention, delirium)	> Anticholinergic tricyclic antidepressants (TCAs) e.g. amitriptyline, dothiepin > Anticholinergic antipsychotics e.g. chlorpromazine, olanzapine > EPSE medication e.g. benztropine
Potential for Hypotension (both postural and non-postural)	> Anti-hypertensives > TCAs

For more information

SA Pharmacy Medicines Information
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