SAFERx
SAFER USE OF HIGH RISK MEDICINES

Waitemata District Health Board
Best Care for Everyone

CLOZAPINE - SAFE PRESCRIBING - WE ARE COUNTING ON YOU

- REGULARLY CHECK FOR SYMPTOMS OF NEUTROPENIA AND AGRANULOCYTOSIS
- ASSESS FOR MYOCARDITIS AND CARDIOMYOPATHY
- MANAGE CONSTIPATION PROACTIVELY
- BE AWARE OF OTHER ADVERSE REACTIONS AND INTERACTIONS WITH CLOZAPINE

Clozapine has drastically improved the lives of patients with resistant schizophrenia, but it can cause many serious side effects that may present first in primary care. Clozapine is associated with a significant risk of neutropenia, which may progress to a potentially fatal agranulocytosis (a reported incidence of 3% and 0.7% respectively)[1] as well as other very serious adverse events.[2]

REGULARLY CHECK FOR SYMPTOMS OF NEUTROPENIA AND AGRANULOCYTOSIS

Please advise patients to be alert for symptoms of neutropenia (eg fever, sore throat or flu-like symptoms). Anyone taking clozapine and presenting with these symptoms needs an urgent full blood count, medical review, and their mental health team notified immediately.[2,3,4,5]

If you have a patient who is taking clozapine, please consider putting an alert on their file to raise awareness that even minor symptoms could be serious.

Everyone taking clozapine must undergo rigorous blood monitoring on a regular basis. Patients are registered with the manufacturer's blood monitoring database ie *ClopineConnect*™ for *Clopine*® brand, or *CareLink Plus*™ for *Clozaril*® brand.[2,3]

Patients treated with clozapine must have a baseline full blood count 10 days prior to commencing treatment, then **weekly** full blood counts for the first 18 weeks of treatment. Monthly monitoring is required throughout treatment and for 4 weeks after discontinuation.[2,3] However, despite this vigilance, deaths from agranulocytosis have occurred in New Zealand.[4]

Be aware there are many medicines that may increase the risk of neutropenia when used concurrently with clozapine such as some antibiotics (eg co-trimoxazole and erythromycin), carbamazepine, and antineoplastics that are associated with bone marrow suppression.[2,3]
It is advisable not to use drugs known to have substantial potential to depress bone marrow function concurrently with clozapine.[3] Clozapine must not be prescribed to patients with bone marrow suppression or to those with a history of clozapine-induced blood dyscrasias.[2,3]

ASSESS FOR MYOCARDITIS AND CARDIOMYOPATHY

Clozapine is associated with a small but significant risk of myocarditis and cardiomyopathy; fatalities have been reported in New Zealand. There is a greater risk of myocarditis within the first 2 months of initiating clozapine,[2,3] whereas, cardiomyopathy usually has a latent onset at approximately 9 months after starting clozapine. Compared to the general population, clozapine-treated patients have a 17 to 322 times greater rate of myocarditis, and a 14 to 161 times greater rate of fatal myocarditis.[6,7]

Symptoms of myocarditis are often non-specific and include (but are not limited to) flu-like illnesses, unexplained fatigue, chest pain, dyspnoea, marked fluctuations in blood pressure, or electrocardiogram changes.[2,3] Maintain a high level of suspicion, especially when starting therapy.[2,3] Patients presenting with any of these symptoms should be referred urgently for a cardiology review.[3,4]

MANAGE CONSTIPATION PROACTIVELY

Clozapine causes constipation in 14 to 60% of patients.[8] There have been several deaths reported in New Zealand caused by complications of severe constipation associated with clozapine.[9]

The risk of severe constipation is increased when clozapine is used concurrently with other medicines that are also constipating, such as anticholinergics (eg tricyclic antidepressants), opioids, and calcium channel blockers.[2,3] Other risk factors include concurrent illness and high doses of clozapine.[8]

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Proactive use of laxatives, dietary advice, monitoring bowel habit, and avoiding drug combinations that exacerbate constipation is recommended.[2,3,4] Prior to initiating clozapine, pre-existing constipation should be addressed. Patients should be warned about the risks of constipation and provided with information about diet, exercise and fluid intake. Symptoms of serious complications include abdominal pain or distension, vomiting, reduced appetite and nausea. Advise patients to report these symptoms immediately.[8]

BE AWARE OF OTHER ADVERSE REACTIONS AND INTERACTIONS WITH CLOZAPINE

Clozapine shares many adverse effects that are common to other antipsychotic medicines, eg sedation and postural hypotension, although the risk of these can be reduced with slow dose titration.[10]

Weight gain and glucose intolerance (leading to type 2 diabetes) may occur.[11,12] Diabetic coma has occurred in patients who were previously non-diabetic. Metabolic changes may increase cardiovascular and cerebrovascular risk.[3] Monitor weight, HbA1c and lipid parameters closely and encourage dietary and lifestyle modifications such as exercise. If necessary, use risk-lowering medications when appropriate, eg statins for elevated lipids.[4]

Other problematic side effects that require ongoing monitoring and management include enuresis,[13] hypersalivation,[14] and tachycardia.[10] There have been individual case reports relating to pancreatitis, thrombosis and hepatic toxicity.

Clozapine also lowers the seizure threshold which can be troublesome at higher doses.[15] Uncontrolled epilepsy is a contraindication to clozapine use.[3]

Interactions

Clozapine interacts with a range of medicines because it is a substrate for CYP450 isoenzymes so care is needed when prescribing inducers or inhibitors of these enzymes.[2,3]

Inducers – may decrease clozapine effect

Concomitant administration of CYP450 inducers may **decrease** the plasma levels of clozapine, eg carbamazepine, phenytoin, rifampicin and omeprazole.[2,3]

Clozapine levels are affected by cigarette smoking, however it is the constituents of smoke, not nicotine itself, that induce liver enzymes and increase the metabolism of clozapine. As a consequence, elevated clozapine levels may occur when patients stop smoking. If patients stop smoking, and are taking high doses of clozapine, it is advisable to monitor plasma clozapine levels, clozapine levels, because a dose reduction may be required.[4,16]

Inhibitors – may increase clozapine effect

Administration of CYP450 inhibitors may **increase** the plasma levels of clozapine, eg erythromycin, ciprofloxacin, and selective serotonin re-uptake inhibitors (SSRIs) such as paroxetine and citalopram.[2,3]

The plasma concentration of clozapine can also be increased by a high caffeine intake (more than 400mg/day). Clozapine levels can subsequently decrease by nearly 50% after a 5 day caffeine-free period.[2,3]

Note: Clozapine can also enhance the central effects of alcohol, CNS depressants, and benzodiazepines.[2,3]

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REFERENCES

1. Alvir J et al. Clozapine induced agranulocytosis. The New England Journal of Medicine 1993;329(3):162-67.
2. Douglas Pharmaceuticals Ltd. Clopine tablets data sheet 19 November 2012. www.medsafe.govt.nz/profs/datasheet/c/clopinetaboralsuspen.pdf (Accessed 10-12-12).
3. Novartis NZ Ltd. Clozaril tablets data sheet 26 June 2012. www.medsafe.govt.nz/profs/datasheet/c/clozariltab.pdf (Accessed 10-12-12).
4. Clozapine: A reminder about safe and effective use. Best Practice Journal 2008;14:12-13. www.bpac.org.nz/magazine/2008/june/docs/bpj14_clozapine_pages_12-13.pdf (Accessed 11-02-13).
5. Monasterio E, McKean A. Prescribing atypical antipsychotics in general practice. Best Practice Journal. 2011;40:14-23. www.bpac.org.nz/magazine/2011/november/docs/bpj_40_antipsychotics_pages_14-23_pf.pdf (Accessed 10-12-12)
6. Medsafe Pharmacovigilance Team. Clozapine and Achy Breaky Hearts (Myocarditis and Cardiomyopathy). Prescriber Update 2008;29(1):10-12. www.medsafe.govt.nz/profs/PUArticles/Clozapine.htm (Accessed 11-02-13)
7. Haas S et al. Clozapine associated myocarditis. A review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia 1993-2003. Drug Safety 2007;30(1):47-57.
8. Clozapine impacts on the colon. Prescriber Update 2011;32(2):14-15 www.medsafe.govt.nz/profs/puarticles/clozapinejune2011.htm (Accessed 11-02-13)
9. Ellis PM, McLean RM, Harrison-Woolrych M. Clozapine: Fatal'constipation' more common than fatal agranulocytosis. Prescriber Update 2007;28(1):7 www.medsafe.govt.nz/profs/PUArticles/clozGI.htm (Accessed 10-12-12)
10. Merrill D, William G, Goff D. Adverse cardiac effects associated with clozapine. Journal of Clinical Psychopharmacology 2005;25(1):32-41.
11. Lamberti J et al. Prevalence of metabolic syndrome among patients receiving clozapine. American Journal of Psychiatry 2006;163(7):1273-76.
12. Lindenmayer J et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical and atypical antipsychotics. American Journal of Psychiatry 2003;160(2):290-96.
13. Warner J, Harvey C, Barnes T. Clozapine and urinary incontinence. International Clinical Psychopharmacology 1994;9:207-09.
14. Praharaj S et al. Clozapine-induced dialorrhea: pathophysiology. Psychopharmacology 2006;185:265-73.
15. Devinsky O, Pacia S. Seizures during clozapine therapy. Journal of Clinical Psychiatry 1994;55([9](Suppl B)):153-56.
16. Ministry of Health 2007. New Zealand Smoking Cessation Guidelines. Wellington. www.health.govt.nz/publication/new-zealand-smoking-cessation-guidelines (Accessed 06-05-2014).

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