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
- MANAGE CONSTIPATION PROACTIVELY
- ASSESS FOR MYOCARDITIS AND CARDIOMYOPATHY
- BE AWARE OF OTHER ADVERSE REACTIONS AND INTERACTIONS – ESPECIALLY SMOKING

Clozapine has drastically improved the lives of patients with treatment resistant schizophrenia, but it can cause serious adverse effects. Clozapine can only be initiated by a Psychiatrist, but symptoms of adverse effects may present first in Primary Care. General Practitioners are involved with on-going prescribing responsibilities within shared care programs in some DHBs (contact your Community Mental Health Team for more information).

Clozapine is associated with neutropenia which may progress to a potentially fatal agranulocytosis (a reported of incidence 3% and 1% respectively).[1] Severe constipation, myocarditis and adverse metabolic effects need to be assessed regularly; these are not always dose-dependent.[1] Close monitoring is essential to reduce the occurrence of potentially fatal adverse reactions.

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.

Regular blood monitoring is necessary for pharmacists to supply clozapine. Patients are registered with the manufacturer's blood monitoring database; *ClopineConnect*™ for Clopine® brand, or *CareLink Plus*™ for Clozaril® brand. General Practitioners who are involved in prescribing will need to use the blood monitoring database; they will be provided with training and access via a web portal.

A baseline full blood count is required 10 days prior to commencing treatment, then **weekly** full blood counts are needed during the first 18 weeks of treatment. 28 day ('monthly') monitoring is required thereafter and for 4 weeks after discontinuation.[2,3] Despite this vigilance, deaths from agranulocytosis have occurred in New Zealand.[4] Agranulocytosis tends to develop during the first 6 months of treatment and is not dose-related. Neutropenia can occur at any time.[6]

Other medicines that can also increase the risk of neutropenia should not be used concurrently with clozapine. These include some antibiotics (eg co-trimoxazole, trimethoprim, nitrofurantoin), carbamazepine, and antineoplastics that are associated with bone marrow suppression.[2,3] Patients with a history of bone marrow disorders should be carefully reviewed by a haematologist prior to initiating clozapine.[2,3]

MANAGE CONSTIPATION PROACTIVELY

Clozapine causes constipation in at least 80% of patients[7] and the onset can occur at any time during treatment.[6] Complications from constipation are the most commonly reported reason for clozapine-induced mortality and serious morbidity in New Zealand. Constipation is underreported and may not be identified even with specific questioning.[7]

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.[6] The use of iron supplements may also increase the risk.

Proactive use of stimulant laxatives,[8] dietary advice, monitoring bowel habit, and avoiding combinations that exacerbate constipation is important.[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. Bulking laxatives are not recommended because they may make existing constipation worse. Symptoms of serious complications include abdominal pain or distension, vomiting, watery diarrhoea (overflow), reduced appetite and nausea. Advise patients and their families to report these symptoms immediately.

Treatment interruption and review is recommended for patients showing evidence of severe constipation.[6]

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Patients with no bowel movement in five days, despite the use of laxatives, should be admitted to hospital for treatment.[6]

ASSESS FOR MYOCARDITIS NAD CARDIOMYOPATHY

Clozapine is associated with a small but significant risk of myocarditis and cardiomyopathy; fatalities have been reported in New Zealand. Myocarditis symptoms generally develop within 1 month of starting clozapine, whereas, cardiomyopathy usually has a latent onset after approximately 1 year of starting, but can occur at any time.[6]

Symptoms of cardiomyopathy include signs of heart failure, flu-like illness, cough, fever, sinus tachycardia, hypotension and chest discomfort.[6]

Symptoms of myocarditis are often non-specific and may include flu-like illnesses, gastrointestinal upset, unexplained fatigue, chest pain, dyspnoea, marked fluctuations in blood pressure, and electrocardiogram changes.[2,3] Compared to the general population, clozapine-treated patients have a 17 to 322 times greater rate of myocarditis.[9] Clozapine-associated myocarditis is not dose-related.[6]

Maintain a high level of suspicion of cardiomyopathy and myocarditis,.[2,3] Patients presenting with any of these symptoms should be referred urgently for a cardiology review,[2,3,4] and the patient's psychiatrist notified. It is likely that clozapine will be stopped;[1] a delayed diagnosis results in worse outcomes.[6]

BE AWARE OF OTHER ADVERSE REACTIONS AND INTERERACTIONS

Clozapine has many adverse effects that are common to other antipsychotic medicines, such as sedation and postural hypotension, but these may be significantly more pronounced if the dose is not gradually titrated or a 'normal' dose is given after a treatment interruption. The risk can be reduced with slow dose titration when starting treatment, and after any treatment interruption[10] of more than 2 days.

As with several other antipsychotics, weight gain and glucose intolerance (leading to type 2 diabetes) can occur.[1,11] Diabetic coma has occurred in patients who were previously non-diabetic. Metabolic changes may increase cardiovascular and cerebrovascular risk.[3] Monitor weight, blood pressure, HbA_{1c} and lipid parameters closely and encourage dietary and lifestyle modifications such as exercise. If necessary, use risk-lowering medications when appropriate, such as statins for elevated lipids.[4] Metformin may be used in those with glucose intolerance if lifestyle interventions alone have failed[12] and may also be considered as an adjunct for weight loss for people experiencing weight gain.[13]

Other problematic side effects that require ongoing monitoring and management include enuresis,[14] hypersalivation,[15] increased sweating[2] and tachycardia.[10] Clozapine has been associated with increased incidence of pneumonia, and pulmonary aspiration.[2,3,16] There have been individual case reports relating to pancreatitis, thrombosis and hepatic toxicity. Clozapine also lowers the seizure threshold which can be troublesome with higher serum levels (see interactions below).[17] 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. Care is needed when prescribing inducers or inhibitors of these enzymes or when there is a chance in smoking habits.[2,3]

Inducers – may decrease clozapine effect

Concomitant administration of CYP450 inducers may decrease the plasma levels of clozapine. These include 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, up to double baseline, may occur when patients stop smoking. If patients stop smoking it is advisable to monitor plasma clozapine levels, dose reduction may be required in conjunction with mental health service advice.[4]

Conversely, if a patient starts smoking during treatment, the therapeutic effect of clozapine may be reduced.[1] It is important that patients are aware of this and report any changes in smoking status during treatment.[1]

Inhibitors – may increase clozapine effect

Administration of CYP450 inhibitors may increase the plasma levels of clozapine. These medicines include erythromycin, ciprofloxacin and selective serotonin re-uptake inhibitors (SSRIs) such as paroxetine and fluoxetine.[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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