CLOZAPINE – Safe and Effective Use

GPs Can Make The Difference

Contributed by Nikki Holmes, Mental Health Pharmacist Coordinator, Waitemata DHB, on behalf of DHBNZ Safe and Quality Use of medicines Group (SQM)

http://www.safeuseofmedicines.co.nz

Clozapine is the gold-standard treatment for people with schizophrenia who are unresponsive to or intolerant of other antipsychotics. It is effective in one-third of people after six weeks[1] and around 60% of people after one year.[2] Unfortunately there can be some significant adverse effects and interactions associated with its use. GPs have a vital role in detecting and managing these.

Significant adverse effects

Constipation – Constipation is common, predictable and is related to anticholinergic effects. Poor diet and inactivity can increase the risk of constipation, which should be monitored for and actively managed. Note that lactulose takes 48 hours to be effective; in some situations this may be too slow. Although helpful when used acutely, ongoing stimulant use (e.g. senna) should be avoided as the bowel will become dependent. Inadequately treated constipation may lead to life-threatening sequelae such as a toxic megacolon – there have been several such cases recorded, all of which have necessitated emergency colectomies. Most people were taking other anticholinergic agents as well as clozapine – this should be avoided wherever possible especially if there is a history of constipation.

Metabolic Syndrome – Weight gain, hyperglycaemia and dyslipidaemia are all associated with clozapine. Relevant parameters should be regularly monitored and diet and exercise interventions made as clinically indicated. It may also be appropriate to use pharmacological management.

Seizure Threshold – Clozapine lowers the seizure threshold dose dependently. If seizure activity develops or pre-existing seizures worsen, this should be followed up. Carbamazepine should not be used with clozapine due to the significant increased risk of blood dyscrasias[3,4] and the effect on serum concentrations.

Blood dyscrasias – These are rare but can be fatal. If a person taking clozapine presents with an infection, a full blood count should be performed to exclude neutropenia/agranulocytosis. Should an antibiotic be indicated it is worth remembering that some are more likely than others to cause blood dyscrasias (e.g. co-trimoxazole) and some may interfere with clozapine metabolism and therefore serum concentrations (e.g. erythromycin).

Myocarditis – This adverse effect is rare but cases have been reported in New Zealand. If a person develops signs or symptoms (e.g. chest pain, shortness of breath) or cardiac insufficiency or a pre-existing cardiac condition worsens, this should be followed up urgently.

There are also some interactions of note with clozapine

Smoking – Cigarette smoke (not nicotine) induces the enzymes that metabolise clozapine. Stopping smoking will cause serum clozapine concentrations to rise and increase the risk of concentration-related adverse effects such as drowsiness and seizures. Stopping smoking should always be planned with the clinical team so that this effect can be monitored for and managed.

Selective serotonin reuptake inhibitors (SSRIs) – Some SSRIs inhibit the enzymes that metabolise clozapine, thereby causing serum concentrations of clozapine to rise. Citalopram is the preferred SSRI in this situation as this does not interact.

References

1. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. Arch Gen Psych 1988;45:789-96
2. Meltzer HY, Bastani B, Young Knon K et al. A prospective study of clozapine in treatment-resistant patients. 1: preliminary report. Psychopharmacology 1989;99:568-72
3. Clozaril® data sheet dated 15/2/06 from www.medsafe.govt.nz
4. Junghan U, Albers M, Woggon B. Increased Risk of Hematological Side-Effects in Psychiatric Patients Treated with Clozapine and Carbamazepine. Pharmacopsychiatry 1993;26:262