Clozapine is N-demethylated to its main metabolite desmethylclozapine primarily by **CYP1A2 and CYP2C19**, with **CYP3A4,CYP2D6, and CYP2C9** playing a **minor role**,  and N-oxidation of Clozapine is mainly related to **CYP1A2, CY3A4**, and flavin monooxygenases (7). The rate of metabolism varies significantly between patients. As a result, clozapine levels can vary widely between individuals receiving the same fixed dose; levels are also affected by patient demographics:

* Gender (approx. 17% higher in women than men)
* Age: levels increase by roughly 4% for every 5 years above 40 years of age and decrease by roughly 4% for every 5 years below 40 years of age.
* Weight: levels decrease by 5% for each 10 kg above 80 kg and increase by 5% for each 10 kg below 80 kg.

Both clozapine and desmethylclozapine (the major metabolite) are reported by the lab.

Clozapine levels typically peak after 1-3 hours and half-life is usually 8-16 hours at steady state (1).   The half-life of desmethylclozapine is approximately 20 hours.

The therapeutic interval (1050 – 1800 nmol/L) is for trough (pre-dose) levels.  The therapeutic interval is only a guide; there is significant variability in both clinical response and likelihood of side effects. Approximately 20% of patients with levels between 750 nmol/L and 1050 nmol/L will show clinical response whereas at least 60% of patients respond when levels are > 1050 nmol/L.

Seizures can occur at low doses during the upwards titration of dose but are more common at higher doses. The upper level associated with CNS toxicity is not well defined (3). Seizures can occur within or even below the therapeutic interval in some patients.

Dose related side effects include sedation and hypotension.

Side effects unrelated to dose include agranulocytosis, myocarditis, cardiomyopathy, constipation/intestinal obstruction, weight gain, and hypersalivation.

Clozapine levels should not be routinely measured; only measure when there is a specific clinical question (indication).

Indications for measuring clozapine include:

1) Poor clinical response to routine doses. Following a change in dose, patients with poor initial response at 6 weeks may respond by 4-6 months.

2) Signs of toxicity or seizures

3) The patient is altering caffeine intake or smoking habit. Note that hydrocarbons from tobacco smoke, not nicotine, induce CYP1A2 (4). Clozapine levels increase within a few days when quitting.

4) Use of medications or substances known to interact with CYP450 system

5) Patients with known or suspected liver disease

6) Suspected non-compliance

Medications or substances that affect clozapine levels via CYP450:

|  |  |
| --- | --- |
| Increase (via enzyme inhibition) | Decrease (via enzyme induction) |
| Caffeine | Chargrilled meat (hydrocarbons) |
| Cimetidine | Carbamazepine |
| Ciprofloxacin | Smoking |
| Fluoxetine | Phenytoin |
| Fluvoxamine | Rifampicin |

Broccoli and brussels sprouts inhibit CYP1A2 and may increase clozapine levels slightly but the effect is clinically insignificant.

  **Monitoring the compliance of clozapine**

* Serum levels should be interpreted in light of previous measurements where available.
* An unexpectedly high clozapine levels should prompt a clinical reassessment. A dose reduction based only on a high clozapine level may cause relapse (3).
* Acute inflammatory states may lead to an increase in clozapine levels (4).

**Interpretation of desmethylclozapine levels:**

Desmethylclozapine level and desmethylclozapine/clozapine ratios should be interpreted with caution.

For trough sampling, desmethylclozapine levels are usually 25 - 90% of the clozapine level.

The ratio of clozapine to desmethylclozapine is fairly stable over time, a large change may be explained by:

* Recent suboptimal compliance,
* Recent change in smoking status or medication affecting CYP1A2
* The sample was not a trough sample.

A desmethylclozapine level double that of clozapine may be due to:

* Suboptimal compliance during the last 24 hours,
* Induction of CYP1A2 (e.g. tobacco smoking), or
* A rapid metaboliser phenotype.

A desmethylclozapine level persistently less than 30% of the clozapine level suggests a poor metaboliser phenotype or the presence of a CYP1A2 inhibitor.

Recent suboptimal compliance may also explain a desmethylclozapine level less than 30%

Patients taking Clozapine are at risk for significant side effects and toxicity,patients MUST be registered with the supplier. The DHB document: “Prescribing and monitoring clozapine treatment” provides guidance. <https://intranet.sharepoint.waikato.health.govt.nz/site/pol/published/Clozapine%20-%20Prescribing%20and%20Monitoring.pdf#search=clozapine>

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