

Clozapine Plasma Levels

**Plasma Levels**

* Blood samples taken for Clozapine plasma levels must be ‘trough levels’ i.e.12 hours after a dose, do not request a plasma level if a dose of Clozapine has been taken within the last 11 hours or is greater than 13 hours ago.
* Please document the reason for taking the clozapine plasma level in the patient’s electronic notes and inform the patient’s consultant if they aren’t the one requesting the test e.g. side effects, adherence problems, stopped smoking, optimising efficacy
* The sample needs to be posted off to ASI Labs in special packaging with a completed Clozapine assay form. The packaging can be obtained from pharmacy or the trust clozapine clinics. It usually takes up to 5 working days to obtain the result electronically.
* For patients new to clozapine take a clozapine plasma level once patient achieves a maintenance dose of clozapine or 300mg/day is reached, whichever is the lower, to guide treatment. Clozapine levels should also be done if the patient stops smoking or at any other time it is clinically indicated e.g. assessing treatment adherence, optimising dosing of clozapine if poor response, patient experiencing side effects.
* The clozapine plasma level results need to be documented on the electronic patient record system by the medicines information pharmacist with an appraisal of the level (e.g. within range, low, high, actions that need to be taken) and who the result has been sent to/discussed with e.g. patient’s consultant.
* The clozapine and norclozapine levels are quoted on results. On average the ratio of clozapine to norclozapine across all doses is 1.32. Norclozapine has a longer half-life than clozapine so it fluctuate less and can be used to indicate recent compliance as it will take longer to decrease than clozapine. The ratio can be used to interpret clozapine plasma results as follows:

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| **Clozapine:norclozapine ratio** | **Explanation** |
| 1.3 (usually the norclozapine level is two thirds of the clozapine level) | Clozapine level taken at correct time and patient adherence is good |
| >1.3 (the clozapine level is getting a lot bigger than the norclozapine level) | The clozapine level could have been taken less than 11 hours since the last dose. The ratio normally gets bigger as the clozapine metabolism becomes saturated at higher levels. This can also occur if an enzyme inhibitor of clozapine is added, smoking is stopped. |
| <1.3 (the clozapine level is getting similar to or is less than the norclozapine level) | The level is taken greater than 13 hours since the last dose. The ratio can be smaller when patients have a low clozapine plasma level e.g. <0.3mg/l. If the clozapine is less than the norclozapine it may indicate some doses have been missed recently as norclozapine takes longer to drop then clozapine. It could also indicate fast metabolism of clozapine, enzyme induction due to starting smoking or taking an enzyme inducing drug such as rifampicin. |

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| **Plasma level (mg/l)** | **Response to clozapine** | **Suggested action** |
| <0.35 | poor | Try to increase dose to give level of 0.35-0.5mg/l |
|  | good | Continue to monitor response. No further action. |
| 0.35-0.5 | Poor | Consider augmentation of clozapine |
|  | good | Continue to monitor response. No further action. |
| 0.5-1 | Poor | Reduce dose to get within 0.35-0.5mg/l (e.g. decrease by 20% and recheck level). Consider augmentation of clozapine. Consider use of prophylactic anticonvulsant if level above 0.6mg/l. Recheck level again after 3 months once in range. |
|  | Good | Slowly reduce dose (e.g. 25mg in week 1, then 25mg in week 2 and then recheck level) to get within 0.35-0.5mg/l. Consider augmentation of clozapine. Consider use of prophylactic anticonvulsant if level above 0.6mg/l. Recheck level again after 3 months once in range. |
| >1 | any | Review urgently. Check for clinical signs of toxicity e.g. severe sedation, falls, seizures. Withhold clozapine for 24hours and reintroduce at a lower dose (e.g. 25% lower). Add anticonvulsant, reduce clozapine dose to reduce level below 1mg/l and consider reducing further down to 0.6mg/l. Consider augmenting clozapine. Recheck level again after 3 months once in range. |

\*the target level is generally considered to be 0.35-0.5mg/l. Please note that an upper limit of 0.6-0.8mg/l is suggested in the Maudsley Guidelines if people haven’t responded to lower levels.

\*\* a prophylactic anticonvulsant should be considered at levels above 0.6mg/l to prevent seizures and myoclonus and should be used when the level nears 1mg/l. If EEG is abnormal above clozapine plasma level of 0.6mg/l add prophylactic anticonvulsant.

\*\*\*please note the above table applies to patients with good adherence, on a stable maintenance dose of clozapine whose plasma levels are taken at the correct time

**Stopping smoking**

**If a patient wishes to stop smoking the following procedure should be followed:**

* **Take a Clozapine plasma level before the patient stops smoking, in order to obtain a baseline. The Clozapine sample should be done as a trough level or 12 hours post dose if the patient is on the drug once a day. The postulated therapeutic range is 350-500micrograms/L (0.35-0.5mg/l). Levels above 600micrograms/L increase the risk of seizure.**
* **Reduce dose by 25% over one week when a patient stops smoking and commence smoking cessation therapy if indicated.**
* **Recheck Clozapine levels after one week and adjust dose according to clinical judgement.**
* **If you find out someone has stopped smoking already then decrease clozapine dose by 25% and arrange a clozapine level within 1-2 weeks.**
* **Please note that until someone smokes less than 7 cigarettes a day the clozapine plasma level wont be affected by a reduction in someone’s smoking as 7-12 cigarettes is probably enough for maximum effect on clozapine levels e.g. going from 40 to 20 cigarettes won’t make a difference to the clozapine plasma level. Once someone gets below 7 cigarettes a day a clozapine level should be taken to guide dosing then a further level taken when they stop smoking cigarettes.**

**The change in plasma level can, in 80% of cases be predicted, using the formula proposed below:**

**Non smoking Clozapine level (micrograms/l) = 45.3 + (1.474 x smoking level micrograms/l)**

**E.g. clozapine dose 400mg/day, clozapine level 360micrograms/l so if stop smoking level will be 45.3 + (1.474 x 360) = 576 micrograms/l.**

**Starting smoking**

* Levels should be monitored as per stopping smoking and doses subsequently adjusted to ensure the plasma level does not become sub-therapeutic ie increase dose to previous smoking dose over at least one week. Repeat clozapine plasma level after one week.

References

Taylor D et al. Maudsley Prescribing Guidelines in Psychiatry. 13th ed

Bazire S. Psychotropic Drug Directory 2018

Bleakley S, Taylor D. Clozapine Handbook. 2013.

Stockley’s Drug Interactions [www.medicinescomplete.com](http://www.medicinescomplete.com) (accessed 25.2.20)

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