Guidance on Clozapine Therapeutic Drug Monitoring

Contents

Background

Clozapine dosage should primarily be adjusted according to the patient's clinical response and tolerability of adverse effects, rather than in response to plasma levels – the principle of "treat the patient, not the levels". However, checking plasma levels (Therapeutic Drug Monitoring, or TDM) is a useful and important tool to optimise treatment in certain situations - see "When would a clozapine assay be helpful?" below.

What is the relationship between dose and plasma level of clozapine?

There is a definite relationship between the dose of clozapine and the levels of clozapine and norclozapine achieved in the plasma (Table 1) although there is a wide (50-fold) variation between patients in the rate at which they metabolise clozapine into norclozapine.

Table 1 – Plasma clozapine and norclozapine levels vs. prescribed dose in 85,958 samples in which clozapine and norclozapine were detected.

Clozapine dose (mg/day)	Number of samples	Observed plasma levels. [median (10th-90th percentile)]	
		Clozapine (mg/L)	Norclozapine (mg/L)
50 - 150	2,632	0.20 (0.06 - 0.55)	0.13 (0.05 - 0.28)
151 - 250	8,338	0.30 (0.09 - 0.72)	0.19 (0.08 - 0.38)
251 - 350	18,794	0.34 (0.13 - 0.79)	0.23 (0.10 - 0.46)
351 - 450	20,677	0.40 (0.16 - 0.90)	0.27 (0.12 - 0.53)
451 - 550	14,504	0.45 (0.19 - 1.00)	0.31 (0.15 - 0.60)
551 - 650	10,509	0.50 (0.22 - 1.08)	0.35 (0.16 - 0.67)
651 - 750	5,507	0.54 (0.23 - 1.16)	0.37 (0.18 - 0.72)
751 - 850	3,129	0.57 (0.25 - 1.25)	0.39 (0.19 - 0.80)
851 +	1,868	0.55 (0.25 - 1.24)	0.41 (0.19 - 0.84)

What does the norclozapine level tell us?

Norclozapine is the major metabolite of clozapine – it is active, but less so than clozapine and does **not** appear to be important when assessing clinical effect. The ratio of clozapine to norclozapine averages 1.25 in populations but may differ between individuals, although it should remain consistent in an individual in the absence of changes to their intake of enzyme-affecting factors. A lower ratio indicates “rapid metaboliser” status, exposure to CYP enzyme inducers or last dose missed, while a higher ratio indicates “poor metaboliser” status, exposure to CYP enzyme inhibitors, a non-trough sample or recent missed doses.

Is there a therapeutic range for plasma clozapine levels?

It is difficult to define a therapeutic range for plasma clozapine levels because of the increase in response observed with duration of therapy. Several studies have suggested that efficacy is associated with ‘trough’ clozapine levels of 0.35 mg/L or above. **An upper limit to the clozapine target range has not been defined.** It has been suggested that a trough level above 0.6 mg/L increases the risk of adverse effects.

Consensus suggests patients who do not appear to be responding to clozapine should have their dose adjusted to achieve plasma levels of at least 0.35 mg/L.

What factors affect plasma clozapine levels?

Factors affecting absorption.

Patient adherence – non-adherence and poor adherence can be assessed by reference to the data presented in Table 1.

Gastro-intestinal absorption of clozapine can be reduced with prolonged diarrhoea, and increased in constipation.

Factors affecting metabolism / clearance.

For a given stable dose, plasma clozapine levels are generally lower in younger patients, males and smokers, due to faster metabolism, and higher in Asians and the presence of liver disease, where metabolism is impaired.

Smoking – starting or stopping smoking respectively decreases or increases plasma clozapine levels and therefore increases or decreases the clozapine dose requirement. The effect on plasma levels can occur quickly, possibly within 2-3 days of the change in habit.

Concurrent medication – plasma clozapine levels are also affected by drugs affecting hepatic CYP enzymes by either induction (e.g. carbamazepine) or inhibition (e.g. fluvoxamine, ciprofloxacin, erythromycin) resulting in a reduction or increase in levels respectively.

Caffeine is both a substrate and weak inhibitor of CYP1A2 enzyme, so competes with clozapine for CYP1A2 metabolism which potentially affects plasma clozapine levels. While the effect of caffeine may not be clinically significant in most individuals, there are case reports of increases in plasma clozapine levels during periods of excessive caffeine intake due to reduced metabolism of clozapine by CYP1A2. In an otherwise stable patient, consistent caffeine intake (low or high) does not require any action in terms of checking plasma clozapine levels or dose adjustment but checking levels in response to a significant change in intake (up or down) is prudent.

Infections – cytokines released in response to infection can inhibit the activity of CYP1A2 enzymes and therefore the metabolism of clozapine; this may result in an increase in plasma clozapine levels. The scale and clinical significance of the effect is dependent on the type, severity and duration of the infection. Certain antibiotics may also have an effect on metabolism (see above)

Factors affecting distribution.

Although weight-based dosing of clozapine is not recommended, significant weight gain or weight loss in patients on established treatment may affect the volume of distribution and therefore plasma clozapine levels.

Are adverse effects related to dose or plasma clozapine levels?

Most adverse effects are related to dose or plasma level. These include seizures, drowsiness, hypersalivation, tachycardia and gastrointestinal hypomotility. They may be avoided by increasing the dose slowly or alleviated by reducing the dose. Neutropenia and agranulocytosis are not dose or plasma level related.

When would a clozapine assay be helpful?

In general, a lower threshold for checking plasma clozapine levels should be applied to patients who are known poor metabolisers, or whose previous levels are higher than expected from the dose being taken (towards or above the 90th percentile in table 1).

Plasma clozapine and norclozapine measurement can be useful in the following situations:

- **Assessing adherence** - total non-adherence in the days immediately preceding venepuncture is easy to diagnose (no/very low clozapine levels detected in plasma). Poor adherence can be assessed by reference to the data presented in Table 1.
- **Poor response** - it may be helpful to assess poor responders after 3-6 months of treatment provided that the dose and influencing factors have been constant for a week or so before sampling. If the plasma clozapine level is less than 0.35 mg/L then dosage increase is warranted. Consider whether co-prescription of enzyme-inducing drugs, e.g. phenytoin, may have resulted in levels lower than expected.
- **With increasing age** – as drug distribution and metabolism change with aging, clozapine dosage should be regularly reviewed in older patients (as a minimum at each 6-month prescription renewal); checking plasma clozapine levels may be helpful to inform appropriate dose adjustments.
- Where a patient has **pneumonia or other serious infection** (generally defined as an infection requiring hospital admission), or a history of elevated levels or increase in side-effects associated with less serious infections.
- Monitoring the effect of changes in tobacco **smoking habit** including switching to an e-cigarette/vape starting or stopping smoking respectively increases or decreases clozapine metabolism and therefore clozapine plasma levels. This effect can occur very quickly, possibly within 2-3 days of the change in habit. It is worth noting that smoking between 7-12 cigarettes per day may be sufficient to cause maximum enzyme induction, therefore an increase in the level of smoking above this amount may have little effect on plasma clozapine levels. See appendix 1 of "Medicines & smoking procedure"
- Diagnosing **dose-related adverse effects**, particularly if:
  - clozapine clearance may have been reduced due to smoking cessation, a significant change in caffeine intake or co-prescription of an enzyme inhibitor (e.g. ciprofloxacin, fluvoxamine);
  - significant weight loss may have affected the volume of distribution.
- Investigating suspected **clozapine self-poisoning/clozapine toxicity**. Useful to establish when to restart therapy in conjunction with advice from the relevant clozapine monitoring service.
- At **doses above 600 mg a day** it may be useful to assess the need for anticonvulsant prophylaxis, which should be considered if clozapine levels exceed 0.6 mg/L (unless EEG is normal),

- To inform an **annual review of treatment,** if clinically indicated by any of the above criteria
- To provide a baseline for **all service users transferred into TEWV services on clozapine**, to allow for informed, continued safe prescribing.

How should plasma clozapine levels be measured and recorded?

Patients taking Clozaril®

Plasma clozapine levels can be measured using the Synnovis pathology service www.synnovis.co.uk . The forms, kits and envelopes can be obtained from the Trust Pharmacy team or the Clozaril Patient Monitoring Service.

Patients taking other brands of clozapine.

Do not use CPMS kits or send samples to Synnovis. Check current arrangements with Trust Pharmacy team

Blood should be sampled into an EDTA tube either immediately before a morning dose (if the patient takes clozapine twice daily, morning and night), or 10-12 hours post dose (if the patient takes clozapine once daily, at night) – i.e. a 'trough' sample. It is important to note the time of sampling after the last dose since this may influence interpretation of the result. To allow for a steady state to be achieved take the blood sample only after the patient has taken the same dose for at least 3 days.

Nominated staff from the relevant team are alerted via email when the results are available. The results must be retrieved and entered into the 'Physical Health' section of the patient's electronic clinical records, and the relevant clinician notified .

What action should be taken in response to clozapine levels?

The table below should be considered as an aid to decision making rather than evidence-based instructions

Plasma clozapine level	Response status	Tolerability status	Suggested action
<0.35 mg/L	Poor[1]	Poor[3]	Increase dose very slowly to achieve level of 0.35 mg/L
	Poor[1]	Good[4]	Increase dose to achieve level of 0.35 mg/L
	Good[2]	Poor[3]	Maintain dose. Consider dose reduction if tolerability does not improve
	Good[2]	Good[4]	Continue to monitor. No action required
0.35 - 0.50 mg/L	Poor[1]	Poor[3]	Increase dose very slowly, according to tolerability, to achieve level >0.5 mg/L. Consider prophylactic anticonvulsant[6]. If no improvement, consider augmentation[5]
	Poor[1]	Good[4]	Increase dose slowly, according to tolerability, to achieve level >0.5 mg/L. Consider prophylactic anticonvulsant[6]. If no improvement, consider augmentation[5]
	Good[2]	Poor[3]	Maintain dose to see if tolerability improves. Consider dose reduction to achieve plasma level of around 0.35 mg/L
	Good[2]	Good[4]	Continue to monitor. No action required.
0.51 - 1.00 mg/L	Poor[1]	Poor[3]	Consider use of prophylactic anticonvulsant[6]. Consider augmentation[5]. Attempt dose reduction if augmentation successful.
	Poor[1]	Good[4]	Consider use of prophylactic anticonvulsant[6]. Consider augmentation[5].
	Good[2]	Poor[3]	Attempt slow dose reduction to achieve plasma level of 0.35-0.5 mg/L unless non-response at lower level is documented. If this is the case, maintain dose and consider adding anticonvulsant. Anticonvulsants[6] should be used in patients whose levels exceed 0.6 mg/L unless EEG normal. Optimise treatment for adverse effects.
	Good[2]	Good[4]	Consider use of prophylactic anticonvulsant[6]. Maintain dose if good tolerability continues.
>1.0 mg/L	Poor[1]	Poor[3]	Add anticonvulsant[6]. Attempt augmentation[5]. Reduce dose to achieve level of <1.0 mg/L Consider abandoning clozapine treatment
	Poor[1]	Good[4]	Add anticonvulsant[6]. Attempt augmentation[5], if successful reduce dose to achieve level <1.0 mg/L. If unsuccessful consider abandoning treatment.
	Good[2]	Poor[3]	Add anticonvulsant[6]. Attempt dose reduction to achieve plasma level <1.0 mg/l.
	Good[2]	Good[4]	Add anticonvulsant[6]. Monitor closely: attempt dose reduction only if tolerability declines.

1. **Poor response:** No or unsatisfactory response to clozapine. Not well enough to be discharged.
2. **Good response:** Obvious positive changes related to use of clozapine. Suitable for discharge to supported or unsupported care in the community.
3. **Poor tolerability:** Dose constrained by adverse effects such as tachycardia, sedation, hypersalivation, hypotension
4. **Good tolerability:** Patient tolerates treatment well and there are no signs of serious toxicity
5. **Augmentation:** Adding another antipsychotic or mood stabiliser
6. **Anticonvulsant prophylaxis:**
    - Seizures are generally dose and plasma-clozapine level dependant, although some seizures occur at low doses during titration.
    - The risk of seizures at higher doses is relatively low - the number-needed-to-harm (NNH) is 166; this means 166 patients with no seizure history would have to be treated with doses >600 mg/day to cause **one** additional seizure compared to doses <300 mg/day
    - Seizures often occur shortly after a dose increase or jump in plasma level, e.g. following addition of an enzyme-inhibitor or removal of an enzyme-inducer.
    - Patients who have tolerated stable high levels for months without seizure activity should not require anticonvulsant prophylaxis.
    - Suitable anticonvulsants are lamotrigine and valproate (see Medication Safety Series 13 for restrictions and requirements in patients under 55 years)

Further advice can be sought from the Trust Medicines Information Service: tewv.medicinesinformation@nhs.net

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