Clozapine and the role of Therapeutic Drug Monitoring

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Background

Clozapine dosage should primarily be adjusted according to clinical response and patient tolerability of adverse effects. It is important to optimise treatment and one of the clinical tools for achieving this is Therapeutic Drug Monitoring (TDM). Measuring clozapine plasma levels may be helpful in certain situations, e.g. partial adherence, assessment of partial response when adherence is good, changes to smoking habits, the addition or stopping of interacting medicines, and when a patient is showing signs of toxicity or severe adverse reactions, and may also inform annual reviews of treatment (for further information see Question "When would a clozapine assay be helpful?", page 2)?

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

There is a definite relationship between the dose of clozapine and the plasma clozapine and norclozapine concentrations (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 concentrations (median, 10th-90th percentile) and prescribed dose in 85,958 samples in which clozapine and norclozapine were detected

Clozapine dose (mg/day)	Number of samples	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. Plasma norclozapine does **not** appear important when assessing clinical effect. The ratio of clozapine to norclozapine averages 1.25 in populations but may differ between individuals. A decrease in this ratio may suggest enzyme induction, while an increase suggests enzyme inhibition, a non-trough sample or recent missed doses.

Is there a therapeutic range for plasma clozapine?

It is difficult to define a therapeutic range for plasma clozapine because of the increased response observed with duration of therapy. Several studies have suggested that efficacy may be associated with 'trough' clozapine concentrations of 0.35 mg/l or above. **An upper limit to the clozapine target range has not been defined.** It has been suggested that trough concentrations above 0.6 mg/l may lead to increased risk of adverse effects.

General consensus suggests patients who do not appear to be responding to clozapine should have their dose adjusted to achieve plasma levels in the range 0.35-0.5 mg/l.

Are adverse effects related to dose or plasma clozapine levels?

Most adverse effects are related to dose or plasma concentration. These include seizures, drowsiness, hypersalivation, tachycardia and gastrointestinal hypomotility. They can 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?

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 clozapine 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 provided that the dose has been constant for a week or so before sampling. If the plasma clozapine concentration is appreciably less than 0.35 mg/l then dosage increase is suggested.
- **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**
- Monitoring the effect of changes in **smoking habit** including switching to an e-cigarette: starting or stopping smoking respectively increases or decreases the clozapine dose requirement. 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 "Guidance on the use of stop smoking products" for more information link
- Diagnosing **dose-related adverse effects**, particularly if:
  - clozapine clearance may have been reduced due to a change in smoking habit;
  - drug-drug interactions are a possibility (e.g. co-prescription of an enzyme inhibitor such as fluvoxamine or an enzyme inducer such as phenytoin);
  - 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 is recommended when levels exceed 0.6 mg/l.
- 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?

Clozapine plasma levels can be measured using Viapath service www.viapath.co.uk . The forms, kits and envelopes can be obtained from the Clozaril Patient Monitoring Service.

Blood should be collected in EDTA tube either immediately before a morning dose (if the patient takes morning and night), or 10-12 hours post dose ('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 dose for 2-3 days.

Nominated staff from the relevant clinic/hospital are alerted via email when the results are available. The results must be retrieved and entered into the patient's electronic clinical records as a 'Physical Health' case note ticking bloods box, and then notifying relevant clinician of the result.

What factors affect plasma clozapine levels?

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

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

Plasma 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. Clozapine levels are also affected by drugs affecting hepatic enzymes by either lowering (inducers e.g. carbamazepine) or increasing (inhibitors e.g. fluvoxamine, ciprofloxacin, erythromycin) levels.

Gastro-intestinal absorption of clozapine can be reduced with prolonged diarrhoea, and increased in constipation, which increases clozapine levels and side-effects such as gastrointestinal hypomotility which in rare cases can lead to fatal GI obstruction.

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 levels.

When should the clozapine concentration be acted on?

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

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

- **Poor response:** No or unsatisfactory response to clozapine. Not well enough to be discharged.
- **Good response:** Obvious positive changes related to use of clozapine. Suitable for discharge to supported or unsupported care in the community.
- **Poor tolerability:** Dose constrained by adverse effects such as tachycardia, sedation, hypersalivation, hypotension
- **Good tolerability:** Patient tolerates treatment well and there are no signs of serious toxicity

- **Augmentation:** Adding another antipsychotic or mood stabiliser
- **Anticonvulsant:** Seizures are dose and plasma-level dependant. Suitable anticonvulsants are valproate (consider risks in pregnancy in women of child-bearing potential) and lamotrigine.

Constipation: Clozapine-induced constipation is dose related.

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

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