

FOR YOUR INPHARMATION



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Clozapine Serum Levels - A Review of the Literature

This is part one of a two-part Inpharmation. The first part reviews clozapine kinetics and the studies examining the “therapeutic threshold” for serum clozapine levels. The second part reviews the efficacy and side effects of higher serum levels.

INTRODUCTION

Traditionally identified as a “gold standard” for atypical antipsychotics, clozapine continues to provide treatment challenges. The absence of alternative therapies, prevalence of side effects and high cost encourages optimal clozapine use.¹ However identifying the individual patient dosage that produces an optimal clinical outcome continues to present challenges.

Clozapine Kinetics^{9,10}

High inter-patient variability but low intra-patient variability has been observed during numerous studies.¹¹ For example, studies indicate a linear relationship between dosage and serum clozapine levels in individual patients.¹² There can be a 45-fold difference in serum clozapine levels on the same dose between patients.¹³

- **Absorption** - Well absorbed from the gastrointestinal tract with peak serum concentrations occurring 2 to 4 hours after oral administration. The rate or extent of absorption is unaffected by food. Studies indicate that 300 mg/d of clozapine produces serum levels between 200 and 600 ng/mL (611 to 1834 nM/L) at steady state.¹⁴
- **Metabolism** - Oral clozapine experiences extensive first pass metabolism, reducing bioavailability to 50%. Two major metabolites are produced, N-oxide and N-desmethyl (norclozapine) derivatives. Apparently derivatives have lower pharmacological activity and toxicity compared to the parent compound.

Studies indicate that the desmethyl derivative is correlated to the serum clozapine level (77%) and increases with duration of treatment and age.³

- **Distribution** – In-vitro plasma protein binding is approximately 95%. Clozapine and metabolites are distributed into a 2-compartment model resulting in a biphasic concentration-time curve. Fitten et al. noted that clozapine pharmacokinetics are consistent with first order absorption that is linear over plasma concentrations of 10 to 1000 ug/L (30.5 to 3058 nM/L).¹⁰ A rapid elimination phase that could represent redistribution is followed by a slower terminal-phase elimination half-life of 11.8 hours.
- Reith et al. studied the kinetics of clozapine and norclozapine overdose. Their data indicated that the conversion of clozapine to norclozapine was a saturable process.¹⁵ In addition; they found individuals accustomed to taking clozapine experienced little sedation despite a significant ingestion of clozapine. Conversely, marked sedation was present in patients not used to taking clozapine.
- **Elimination** - Urinary and fecal excretion accounts for 49% and 38% of an oral dose of clozapine respectively. Forty-six percent of an oral dose will be eliminated over a 120-hour period. Unchanged clozapine accounts for 2 to 5% of excreted drug. The mean elimination half-life (T1/2) is approximately 12 hours (range 6 to 33 hours).
- Low serum clozapine levels may be due to an inadequate dosage, poor absorption or rapid metabolism.¹ Factors that contribute to this effect include age, gender, weight and smoking pattern. Women can have higher serum clozapine levels than men.¹⁶ Smoking has been associated with lower serum clozapine levels.¹²

- Examples of agents that increase serum clozapine levels include selective serotonin reuptake inhibitors (fluvoxamine and fluoxetine) and antibiotics such as erythromycin. Conflicting reports are available for the addition of valproic acid to clozapine. Agents that induce the CYP1A2 metabolic pathway such as carbamazepine and cigarette smoking decrease serum clozapine levels.

Therapeutic drug monitoring (TDM) may offer an advantage in the management of clozapine patients. Clozapine meets many of the required criteria when considering TDM; identifiable therapeutic range, high inter-individual but low intra-individual variability in bioavailability and half-life, potential for clinically relevant drug interactions and risk of patient non-compliance.

Minimum Effective Concentration

Early studies were unable to identify a relationship between serum clozapine levels and therapeutic effect.^{12,17,18,19,20,21} The methodology used in these trials had a number of problems: small numbers of patients, no or short fixed-dose periods, different analytical procedures within the same study for serum levels and an absence of blinding.

More recent, rigorous studies have suggested the presence of an optimal serum clozapine level (Table 1). Perry et al. used a receiver operator curve (ROC) to identify an optimum clozapine concentration of 350 ng/ml (1070 nM/L).¹¹ Total serum clozapine concentrations, combined clozapine and norclozapine levels, of less than 450 ng/ml (1376 mM/L) predicted non-response in 77.8% of patients.

The “strict” improvement criteria required for the BPRS scores may have confounded the results by limiting the number of identified responders.

A study by Hawegawa et al. supported Perry’s work.¹ Severely ill patients required increased dosages therefore high dosages were negatively associated with outcome. In addition, high, final BPRS scores were associated with low serum clozapine levels and positively related to dosage and baseline BPRS values. High serum clozapine concentrations were associated with a better response to treatment. **The 6-month duration of the study allowed investigators to investigate response and serum levels in slow responders to clozapine.** Additional information about long term

response was provided by the Miller et al. study.²² Miller’s group followed Perry’s original 29 patients for an additional 2-1/2 years. At the end of the Perry study, individual patient dosages were adjusted based on clinical response. **As a result, the patient response rate increased from 38 to 58%. The majority of patients converted to responders by 6 months. In addition, 5 out of 7 non-responders became responders when their serum clozapine levels were increased over 350 ng/mL (1070 nM/L).** A further investigation of plasma clozapine concentrations by Potkin et al. titrated patients to 400 mg/d of clozapine and maintained that dosage for the balance of 4 weeks.¹³ At 4 weeks, patients were randomly assigned to a 400mg/d or 800mg/d group. At 4 weeks clinical response was noted in 60% of patients with serum clozapine levels above 420 ng/ml (1284 nM/L). During the second phase of the study, increased dosage and increased serum clozapine levels in nonresponders resulted in an increased response rate. **When the response rate between the two groups was compared, it was apparent that the increased response rate was greater than what would be expected from time alone.** A six-week investigation of 45 schizophrenic or schizoaffective inpatients refractory or intolerant of antipsychotics.²³ **A ROC and chi-square analysis with Pearson’s correction associated clinical response with serum clozapine levels greater than 350 ng/mL (1070 nM/L).** Another prospective twelve-week study randomly assigned 56 schizophrenic patients to one of three serum clozapine levels; 50-150 ng/mL (153-459 nM/L), 200-300 ng/mL (612-917 nM/L) and 350-450 ng/mL (1070-1376 nM/L).²⁴ All three serum level ranges demonstrated a significant improvement in the BPRS from baseline. **A greater percentage of patients responded to medium to high serum level ranges (60 and 61%) than responded to the low level range (39%).** The authors believed that serum clozapine levels above 250 ng/mL (764 nM/L) did not improve clinical outcomes. They explained that the difference in their serum clozapine levels compared to the previous studies might be due to a number of factors including; dosing schedules, time from last dose and non-linear kinetics at higher dosages.

In an attempt to determine if increasing serum clozapine levels would improve the clinical response, Buckley et al. studied 19 schizophrenic

outpatients.²⁵ All patients had been treated with clozapine for at least 6 months, were considered partial responders and had serum clozapine levels < 370 ng/ml (< 1131 nM/L). Unfortunately increased clinical response was not associated with increased dosage or serum clozapine levels. **The authors concluded that increasing the clozapine doses and serum levels offered no advantage to patients that have previously responded to clozapine.** Spina et al. studied serum clozapine and norclozapine levels in 45 treatment resistant patients.²⁶ Serum clozapine levels of 350 ng/mL (1070 nM/L) separated responders from non-responders with a sensitivity of 72% and specificity of 70%. At serum clozapine levels of 400 ng/mL (1223 nM/L) sensitivity decreased to 67% and specificity increased to 78%. **However, the authors observed a substantial increase in side effects with serum clozapine levels higher than 350 ng/mL (1070 nM/L).**

Fabrazzo M et al. studied the relationship between the time course of clinical response and serum clozapine and clozapine-N-oxide levels.²⁷ The responder's mean serum clozapine levels tended to increase until clinical response then stabilized over time. Non-responders had mean serum clozapine levels less than 260 ng/mL (795 nM/L). **The authors postulated that the continued increase in serum clozapine levels observed in the responders occurring after the final dose titration at 6 weeks may have been due to the conversion of extensive metabolizers to poor metabolizers.**

Summary

These studies have identified a linear relationship between dosage and serum clozapine up to 1000 ug/L (3058 nM/L). However serum clozapine levels for individual patients can vary as much as 45-fold on the same dose. Several "not so recent studies" have identified a "threshold" plasma concentration for clinical response. However, it is important to remember that some patients respond at lower serum clozapine levels. Part two of this Inpharmation will review the efficacy and side effects of higher serum levels.

Written by: Debbie Thompson, Pharm. D.

Reviewed by: Sylvia Zerjav, Pharm. D.

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