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Clozapine Serum Levels - A Review of the Literature

This is part two of a two-part Inpharmation reviewing the literature on serum clozapine levels. This part reviews the efficacy and side effects of higher serum levels.

Manufacturer recommended dosage ranges are usually derived from registration studies submitted to the FDA during the drug approval process. These registration studies generally exclude patients with significant co-morbid disease states or history of treatment resistance and may not reflect the diversity present in the general patient population.

In practice, clozapine is initiated at a low dose and gradually increased until the patient reaches the recommended maximum dosage, achieves significant improvement, or develops unacceptable side effects. First-episode or early stage schizophrenic patients and the elderly may respond to lower clozapine dosages.[2] Patients with a slow or inadequate response may receive higher doses (Table 2).[3] A slow response pattern complicates patient management. Studies in treatment resistant patients identified a 30% response rate at 6 weeks compared to a 71% response rate at 12 months.[4,5]

Table 2. Patients Likely to Receive High Doses[3]
Treatment refractory schizophrenics
Patient with breakthrough symptoms
Partial responders
Rapid metabolizers
Special populations (i.e. developmentally disabled, imprisoned, institutionalized)

In addition to age or disease state, dosing may need to be adjusted for factors such as concomitant medications or genetics. An inadequate therapeutic response or the presence of co-morbid medical conditions may result in the use of concomitant medications. These adjunctive agents may influence serum clozapine levels. Studies indicate that Asians require lower antipsychotic dosages compared to Western populations.[6] Reports from Central Europe indicate that clozapine dosages (200 to 300 mg/d) are significantly lower than the U.S.[7]

Finally, trends in antipsychotic prescribing practices can shift based on clinical experience. For example, a review of clozapine prescriptions in the New York State Office of Mental Health hospital system identified a decrease in the mean daily dose and percentage of patients requiring high dose clozapine between 1997 and 2001 (Table 3). [8]

Table 3. Clozapine Prescribing in New York State[8]

	1997 (1st quarter)	2001 (3rd quarter)
Mean daily dose (mg)	586.3 (n=845)	494.7 (n=851)
Patients using CLZ doses >1000 mg/d	4.5%	0.2%

Is There An Upper Limit?

An upper limit for serum clozapine levels has not been clearly identified. Perry et al observed that the ROC analysis did not suggest an upper limit for serum clozapine levels and therapeutic response. They felt the upper limit would be identified by adverse effects.[11] Hasegawa et al. noted that serum clozapine levels above 370 ng/mL (1131 nM/L) were not essential for clinical response.[1] A study by

Buckley et al. concluded that increasing serum clozapine levels above 370 ng/mL (1131 nM/L) in responders was unlikely to improve the clinical response.[25] VanderZwaag et al. supported these observations.[24] In addition, they could not identify an advantage for the 350-450 ng/L (1070-1376 nM/L) range compared to the 200-300 ng/L (611-917 nM/L) range. The authors believed that differences in study methodology explained the discrepancy between their optimal serum level and the levels identified by other investigators. In addition, they concluded that the "optimal" or "break-point" levels should be regarded as "estimates". Serum levels above these "estimates" would not increase the rate or degree of clinical response but would increase toxic adverse effects. A study by Spina et al observed that the incidence of adverse effects was twice as high at serum concentrations above their optimal level of 350 ng/mL (1070 nM/L) compared to lower serum concentrations.[26]

A separate study compared 23 patients on "high dose" clozapine (900 mg/day) to 13 patients receiving 554 mg/day (± 125 mg).[28] Both groups had similar BPRS and Quality of Life Scores (QLS) but the 'high dose' group were significantly impaired on the Global Assessment Scale (GAS) (48 ± 6 vs 52 ± 9, $p < 0.05$).

Ulrich et al investigated the relationship between therapeutic drug monitoring (TDM) of serum clozapine levels and relapse. Relapse serum clozapine levels ranged from 198-211 ng/mL (594-633 nM/L).[29] Intoxication occurred at serum clozapine levels between 900-2900 ng/mL (2700-8700 nM/L). The risk of intoxication increased at serum clozapine levels greater than 750 ng/mL (> 2250 nM/L). The risk of increased serum levels was more likely to occur in aged, women and non-smokers.

Side Effects At Higher Serum Levels

Olesen et al used a cross-sectional study of 30 chronic schizophrenic inpatients and outpatients to study clozapine serum levels and side effects.[3] All patients were treated with clozapine for at least 3 months and were on the same dosage regime for 2 months. The most common side effect was EEG changes (83%). Increased liver enzyme activity (60%), tachycardia (23%), orthostatic hypotension (17%) and leucocytosis (17%) were also observed.

Table 4. Common Side Effects of Clozapine Treatment[3]
Sedation, hypersalivation, orthostatic hypotension, tachycardia, changes in ECG and EEG, increased liver enzyme activity

Central nervous system adverse effects such as confusion, delirium, and generalized seizures appear to be dose related**.** Seizures occur in 1, 2.7 and 4.4% of patients on doses of <300 mg/d, 300 to 600 mg/d and > 600 mg/d, respectively.[30]
A study comparing clozapine dosage and adverse effects in Innsbruck (Austria) to New York (U.S.) found the mean clozapine dose in Innsbruck was 298 mg/d with a zero incidence of confusion and seizures.[7] By comparison, the mean clozapine dose in New York was 600 mg/d with a 14 % incidence of confusion, and 7.1% incidence of seizure. Simpson et al. reported the serum clozapine levels of two patients experiencing grand mal seizures were 1313 and 2194 ng/ml (4015 and 6709 nM/L).[31] Ten days of erythromycin treatment in a clozapine patient increased serum clozapine levels from 700 to 1300 ug/L resulting in a seizure**.**[32] Haller and Binder reported on four patients that experienced seizures while on clozapine treatment[33] One patient had a pre-existing seizure disorder, the remainder of the patients were on doses of clozapine greater than 600 mg/d.

Table 5. Risk Factors For Seizure Activity[33]
Organic pathology, polypharmacy, rapid dose increases and high doses

A number of investigations have been unable to identify a relationship between serum clozapine or metabolite levels and leucocyte counts.[34,35]

Clozapine Toxicity

The severity of poisoning appears to be related to prior exposure and tolerance. Clozapine poisoning usually presents with CNS depression and

delirium. Seizures may occur in up to 8.8% of cases. Cardiac effects include tachycardia, atrioventricular block, extrasystoles, ventricular fibrillation, and prolongation of the ST segment. Other overdose symptoms include sialorrhea, dysarthria, decreased gag reflex, loss of conjugate eye movements, decreased bowel sounds and decreased power globally. Aspiration pneumonia is a major complication of clozapine poisoning. The mortality rate in overdose is 12%.

Table 6. Common Symptoms of Clozapine Intoxication[33]
Coma, lethargy, tachycardia, agitation and confusion

Summary

Although studies indicate a linear relationship between dosage and serum clozapine up to 1000 ug/L (3058 nM/L) in individual patients, there can be a 45-fold difference in serum clozapine levels on the same dose between patients. 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, while higher levels are associated with an increased incidence of serious side effects. As a result, the manufacturer of clozapine (Novartis-private communication), recommends an upper serum clozapine level of 1000 ng/mL (3058 nM/L) based on the increased risk of CNS adverse effects.

Patients treated with clozapine for an adequate length of time with an inadequate response and serum clozapine levels less than 350 ng/mL (1070 nM/L) may improve their clinical outcome by increasing the clozapine dose to achieve “threshold” plasma concentrations with appropriate monitoring. The caveat would include, *as side effects permit.*

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Table 1. Studies Evaluating Serum Clozapine Concentrations

Study (date)	n	Duration	Dose Titration	Therapeutic Concentration ng/mL	Therapeutic Concentration nM/L	Threshold Response Rate (%)	Result
Perry et al. (1991)[11]	29	4 weeks	400 mg/d or maximum tolerated dose (mean daily dose 384 ± 42 mg)	> 350	> 1070	63 (sensitivity) 77.8 (specificity)	ROC • 22% of patients responded at levels < 350 ng/ml
Hasegawa et al. (1993)[1]	59	6 months	Individual optimal dose (average dose 443.8 ± 270.7 mg/d)	> 370	> 1131	53.3 (sensitivity) 72.7 (specificity)	ROC & discriminate function analysis • 46.7% of patients responded at levels < 370 ng/ml
Miller et al. (1994)[22]	29	21/2 year follow-up		> 350l	> 1070		58% of patients are responders
Potkin et al. (1994)[13]	58	12 weeks	Group 1 & 2 400 mg/d for 4 weeks then Group 2 to 800 mg/d	> 420	> 1284	60	Discriminate function analysis • 8% of patients responded at levels < 420 ng/ml
Kronig et al. (1995)[23]	45	6 weeks	500 mg/d for 21 days if clinically indicated increase to 900 mg/d (average dose 483.9 mg/d)	> 350	> 1070	55	ROC • 8% of patients responded at levels < 350 ng/ml
VanderZwaag et al. (1996)[24]	56	12 weeks	Dosage individually titrated to reach 3 dosage ranges	>200-300 ng/ml	> 616-917 nM/L	60	
Buckley et al. (1997)[25]	19	6 weeks	Dosage increased 20% over baseline				• 9/11 (81%) of patients that increased their dosage had serum levels > 370 ng/ml (1131 nM/L)
Spina et al. (2000)[26]	45	12 weeks	Up to 500 mg/d	> 350l	1070	62	Incidence of side effects was 38% for levels > 350 ng/ml compared to 17% for levels < 350 ng/ml

ROC = receiver operator analysis, Clozapine 1 nM/L = 0.327 ng/mL, Norclozapine 1 nM/L = 0.313 ng/mL

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