

Clozapine levels: navigating infection and interactions in a treatment refractory patient

Lesley Smith

Pharmacy Dept, Princess Alexandra Hospital, Brisbane, Queensland

Objective

To describe the management of clozapine dosing in a patient with a long history of treatment resistant schizophrenia, complicated by fluctuating levels, repeated infection and concurrent ciprofloxacin treatment.

Clinical Features

- 52-year-old male
- *Non-smoker*
- Admitted to an older person mental health ward with an acute relapse in mental state and a psychiatrically complex presentation
- Clozapine dose on admission – 300mg nocte
- Extended admission complicated by recurrent urinary infections and treatment refractory illness
- Indwelling catheter in situ

Relevant Pathology

- Diagnosed with Prostatic Abscess and Urosepsis – *E. Faecalis* and *Pseudomonas* – *ciprofloxacin* treatment recommended (see Figure 1)

Figure 1: Recommendation for ciprofloxacin treatment

51yo
Urosepsis - *E. faecalis* and *Pseudomonas*
Small prostatic abscess - on IV Piptaz

Thanks to Urology and Psych for ongoing review

Nil further fevers
WCC 7.7
CRP 24

Nil new concerns.

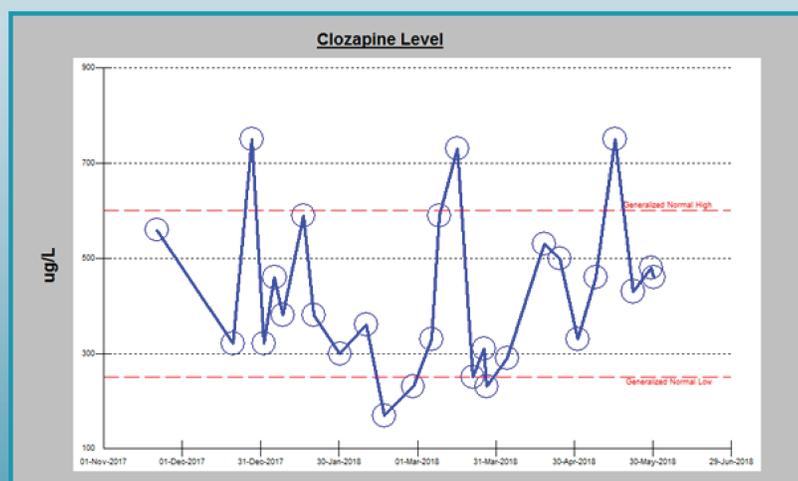
OE:
Temperature 36.7 (11:51)
Systolic Blood Pressure 148 (11:51)
Diastolic Blood Pressure 105 (11:51)
Pulse 88 (11:51)
SpO2 96 (11:51)
Respiratory Rate 19 (11:51)

Impression: Stable

Plan:
Switch to oral Cipro and Augmentin for 6/52 total duration Ab therapy.
Change IDC today to 16Fr

- Recurrent infections throughout admission:
 - o Dec 2017 – Urosepsis
 - o March 2018 – Urosepsis
 - o April 2018 – Urinary Tract Infection (UTI)
 - o May 2018 – Urinary Tract Infection (UTI)
- Clozapine levels fluctuated throughout admission (see Figure 2):

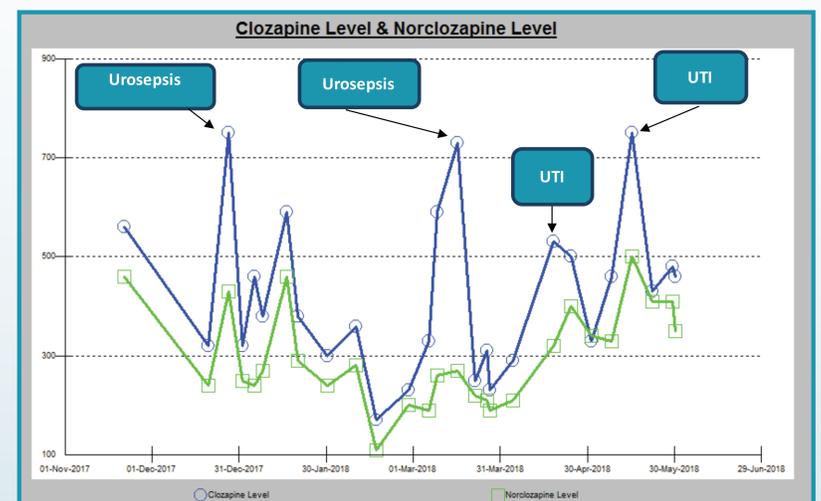
Figure 2: Clozapine levels November 2017 – June 2018



Discussion

- Clozapine is metabolised to norclozapine predominantly via cytochrome P450 enzyme CYP1A2.¹
- Elevated clozapine plasma levels (>1000 ug/L) can lead to over-sedation and an increased risk of seizures.¹
- The addition of ciprofloxacin, a strong inhibitor of CYP1A2, required pharmacist intervention, cessation of clozapine dose titration and careful clozapine plasma level monitoring
- After ciprofloxacin cessation, clozapine levels continued to fluctuate, particularly increasing during periods of concurrent infection, and the treating team was concerned with the safety of managing the required clozapine dose titration.
- Increases in inflammatory mediators (IL-6, TNF-alpha, interferon and CRP) during infection have been linked to a reduction in CYP1A2 expression, causing decreased clozapine metabolism.^{1,2}
- Elevated clozapine levels in infection may not necessarily correlate with toxicity, as it is postulated that an increase in alpha-1 acid glycoprotein (AGP) during infection can increase binding and inactivation of clozapine in the plasma.^{1,3}
- The pharmacist in the team review discussed this association between the presence of infection and the temporarily elevated clozapine levels, highlighting that an enzyme inhibition process may be occurring as shown by the patient's relatively unchanged norclozapine levels. (see figure 3).
- As the patient was not showing signs of toxicity and the levels remained within safe limits (<1000ug/L), the pharmacist advised against unnecessary dose reductions and encouraged cautious dose titration once the infections had cleared.
- The patient's clozapine dose was safely titrated up to 500mg throughout the admission despite the repeated infections and sodium valproate was added for both clozapine augmentation and seizure prophylaxis.

Figure 3: Clozapine and Norclozapine levels with infection



Conclusion

- All pharmacists should be aware of the need to interpret elevated clozapine levels in the context of infection as well as drug interactions.
- Clozapine is the most effective medication for treatment resistant schizophrenia and care is required when advising on dose adjustments, balancing patient safety without compromising patient progress.⁴
- Mental Health pharmacists have an important role in interpreting clozapine levels and advising on dose adjustments.

References

1. Clark, SR et al. Elevated clozapine levels associated with infection: A systematic review. *Schizop Res* 2018; 192:50-56.
2. De Leon, J. Respiratory infections rather than antibiotics may increase clozapine levels: a critical review of literature. *J Clin Psychiatry* 2004; 65(8): 1144-5.
3. Leung JG et al. Infection and inflammation leading to clozapine toxicity and intensive care: a case series. *Ann Pharmacother* 2015; Jun;48(6): 801-5.
4. Siskind, D et al. Clozapine v first- and second-generation antipsychotics in treatment-refractory schizophrenia *Br J Psychiatry* 2016; 209(5): 385-392.