



# Is there a relationship between acute inflammatory stress and clozapine levels?

Abigail Wagner, M.D., Mujeeb U. Shad, M.D., M.S.C.S.

Good Samaritan Regional Medical Center, Department of Psychiatry, Corvallis, OR

## INTRODUCTION

- Clozapine is a gold-standard to manage treatment-refractory schizophrenia.
- However, it has not been accepted as a first line treatment due to serious adverse effects including agranulocytosis and lowering of seizure threshold.
- Although these adverse effects are rare, they are well known and closely monitored.
- There is less awareness of the risks associated with different types of drug interactions, including drug-disease interactions, in which an acute medical stress can alter the plasma level of drugs.

## CASE HISTORY

- This patient is a 51 year old male with treatment-refractory schizoaffective disorder, bipolar type who was stable on 450 mg a day of Clozapine.
- He presented with flu-like symptoms and unyielding auditory hallucinations. This evolved into acute delirium. He was admitted to the medical floor for treatment of severe sepsis, bacterial pneumonia and potentially meningitis.
- Due to severe agitation and aggression, he was given haloperidol and soon after developed NMS requiring ICU admission.
- Surprisingly, a clozapine level ordered 60 hours after the last dose of 250 mg revealed a total clozapine level of 1242 ng/mL

## REPORT OF LITERATURE

- Smoking cessation less than 2 weeks is unlikely to be the cause of toxic levels of clozapine. (6).
- Drug interactions with metoprolol and haloperidol as well as other concomitant medications (i.e., analgesics, antibiotics) are unlikely to be the sole cause. (5)
- Literature review reveals two plausible mechanisms underlying the unusual increase in clozapine levels in patients during acute inflammatory stress:
  - 1) Stress-induced increase in clozapine-binding plasma protein, alpha-1-acid glycoprotein (AAG). (4)
  - 2) Inhibition of CYP1A2, responsible for 70% of Clozapine's metabolism (1) by stress-induced increase in proinflammatory markers, such as interleukin-6 (2), IL-1 beta, TNF alpha, and alpha or gamma interferons. (4)
- In one report, clozapine decreased by a factor of 2, specifically during a respiratory infection. (1)
- In another study, measuring the concentration per dose of antipsychotics in the setting of elevated CRP, clozapine increased by 48% compared to risperidone (24.2%) and quetiapine (11.9%). (3)

	Clozapine Dose	Clozapine (CLZ) levels	Norclozapine (NCLZ) levels	CLZ/NCLZ ratio	Concomitant Medications	Clinical Condition	Location	Smoking Status
In 2018	450 mg/d	333ng/mL	200 ng/mL	1.67	<b>Scheduled:</b> -Atorvastatin 20mg; -Vitamin D3 2,000 IU; -Lurasidone 60mg; -Olanzapine 10mg PRN only once	Medically stable	Inpatient Psych	No smoking; on nicotine patch; pt started smoking as an outpatient
10 months later	450 mg/d	NA	NA	NA	Same as above without lurasidone (Dc'd)	Severe headache	Outpatient	Smoking 1PPD
Next day	250 mg/d	NA	NA	NA	(Evening) Last clozapine dose - 250 mg PO HS <b>Scheduled:</b> -Acetaminophen 2,000 mg -Piperacillin -Tazobactam 4.5 g	Severe headache AMS Blood culture (+) for Pneumococcus; T 102.6F, HR 117 bpm and BP 146/77 mmHg.	Outpatient; Admitted Inpatient Medicine Floor (Evening)	Smoking 1PPD
Next day	Dctd.	NA	NA	NA	<b>PRN:</b> (Evening) Haldol 5mg IV (Evening) Haldol 5mg IV <b>Scheduled:</b> -Vancomycin 2,000mg; -Azithromycin 500mg; -Ceftriaxone 1,000mg; -Metoprolol 25mg; -Nicotine patch 14mg; -Acetaminophen 650mg; -Lovenox 40mg	Continued AMS, worsening HTN, persistent fever – diagnosed with bacterial pneumonia	Inpatient Medicine Floor	No smoking
Next day	Dctd.	NA	NA	NA	<b>PRN:</b> (Morning) Haldol 5mg IV (Morning) Haldol 5mg IV (Afternoon) Haldol 5mg IV <b>Scheduled:</b> -Vancomycin 2,000mg; -Azithromycin 500mg; -Ceftriaxone 1,000mg; -Metoprolol 25mg; -Nicotine patch 14mg; -Acetaminophen 650mg; -Lovenox 40mg	-Patient begins writhing, -Severe rigidity -(Morning) CK >3200 U/I	Inpatient Medicine Floor	No smoking
Next day	Dctd	88 ng/mL	353 ng/mL	2.52	<b>Scheduled:</b> -Acyclovir 1460mg; -Azithromycin 250mg; -Ceftriaxone 4g; -Enoxaparin 40mg; -Lorazepam 1mg; -Vancomycin 1750mg; -Tylenol 325mg; -Dilaudid 0.5mg; -Nicotine 14mg patch; -Dantrolene 245 mg	Continued AMS, HTN, persistent fever, writhing, persistent rigidity. Diagnosed with NMS. CSF cell count indicated pneumococcal meningitis	Inpatient Medicine Floor	No smoking
5 days later	Dctd	<100 ng/mL	<100 ng/mL	NA	<b>Scheduled:</b> -Acyclovir; -Azithromycin; -Ceftriaxone; -Enoxaparin; -Ketorolac; -Phytonadione (vitamin K); -Lorazepam; -Vancomycin; -Tylenol; -Dilaudid; -Lorazepam; -Nicotine	Cleared sensorium, mental status intact, normal vital signs, no rigidity	Inpatient Medicine Floor	No smoking

## DISCUSSION

- Initially, we ruled out other potential reasons for the persistently elevated clozapine levels even after 60 hours of its discontinuation, such as smoking cessation and drug-drug interactions.
- This leaves two possible mechanisms to explain increased clozapine levels in this patient:
  - The first is the changes in clozapine protein binding during an acute inflammatory stress.
  - The second is the CYP enzyme inhibition by the pro-inflammatory markers, such as IL-6

## CONCLUSIONS

- This case exemplifies complex interplay between clozapine pharmacokinetics and acute inflammatory stress secondary to acute bacterial infections.
- Although the adverse effects from toxic clozapine levels in our patient are difficult to separate from those caused by acute medical comorbidities, monitoring of clozapine levels during acute bacterial infections may help detect clozapine toxicity and help prevent further complications.

## REFERENCES & ACKNOWLEDGEMENTS

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AMS (altered mental status); HTN (hypertension); CSF (cerebral spinal fluid); NMS (neuroleptic malignant syndrome); CK (creatinine kinase); PPD (Packs per day); BPM (beats per minute).