

A case report on the effects of COVID-19 on ANC monitoring in a patient on long-term clozapine treatment

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Abstract

Background: Clozapine carries a US boxed warning for severe neutropenia, and strict monitoring is required through the FDA's Risk Evaluation and Mitigation Strategy (REMS) program. Patients with confirmed diagnosis of COVID-19 are also at risk for neutropenia. For patients on clozapine, the diagnosis of this novel virus may require an increase in the frequency of scheduled ANC monitoring. A case report of moderate neutropenia following COVID-19 diagnosis that required an increase in the frequency of ANC monitoring in a patient on long-term clozapine treatment is discussed.

Case Report: A 33-year-old white man with schizophrenia had been on clozapine for more than 2 years, with an ANC monitoring schedule once every 4 weeks. The patient was admitted to the hospital for worsening aggressive behavior. On day 11 of hospital admission, he tested positive for COVID-19. Five days following this diagnosis, the patient's ANC dropped from 2.2/L to 0.8/L. This decrease led to daily ANC labs and the clozapine regimen being held for 1 day. Throughout the patient's admission adjustments were made to the frequency of lab monitoring based on fluctuations in his ANC levels.

Discussion: There have been limited case reports on patients receiving clozapine experiencing neutropenia following the diagnosis of COVID-19. To the authors knowledge, this is the first case report from the United States that specifically discusses the required changes to ANC monitoring.

Conclusions: Patients on clozapine who test positive for COVID-19 may be at an even greater risk for neutropenia, compared with clozapine patients without COVID-19. Increasing the frequency of ANC monitoring should be considered in the weeks following the diagnosis to ensure that clozapine treatment can be safely adjusted, or even discontinued.

Keywords: clozapine, COVID-19, coronavirus, neutropenia, ANC monitoring, schizophrenia

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Background

Clozapine is an atypical antipsychotic that is FDA approved for treatment-resistant schizophrenia. It has been proven effective

when other agents fail, but the potential for serious side effects has led to much caution with its use. The American Psychiatric Association guidelines recommend that clozapine be used in patients with treatment-resistant schizophrenia, specifically if the risk for suicide or aggressive behavior remains significant despite other treatments.¹ Because of the associated risks with clozapine, strict monitoring is required throughout the course of treatment. Currently in the United States, a Risk Evaluation and Mitigation Strategy (REMS) program is required by the FDA to monitor patients on clozapine for severe neutropenia, which is defined as ANC <0.5/L.² Providers are required to



report patient's ANC to the REMS safety program, and follow the guideline provided on how frequently to monitor the patient's ANC levels. ANC is monitored weekly for the first 6 months following clozapine initiation and then every 2 weeks from months 6 to 12. After the patient has been on the clozapine regimen for a year and their ANC level has remained within acceptable range, monitoring is extended to every 4 weeks. Frequency of ANC monitoring is increased in the setting of neutropenia, based on the patient's ANC level.³

Following the onset of the novel COVID-19 virus, there have been limited reports of patients stable on clozapine experiencing neutropenia.⁴ This may present challenges to patients on a stable clozapine regimen and could require changes in the frequency of ANC monitoring. We present a case report of moderate neutropenia following COVID-19 diagnosis that prompted holding clozapine treatment for a short period of time and increasing the frequency of lab monitoring.

Case Report

A 33-year-old white man with schizophrenia and intellectual and developmental disabilities (IDDs) was admitted to a community hospital emergency department (ED) in January 2022 from an assisted living facility because of worsening aggressive behavior mainly due to IDD. The patient had been on clozapine for more than 2 years, stabilized on a regimen of 200 mg 3 times daily. He was also taking fluvoxamine 50 mg daily, levetiracetam 500 mg twice daily, oxcarbazepine 300 mg twice daily, and perphenazine 2 mg daily, which were continued upon admission. Per the REMS program, white blood cell count and ANC were monitored every 4 weeks, with ANC labs prior to hospitalization 2.888/L in January 2022 and 1.872/L in December 2021. On day 4 of admission the patient's clozapine and norclozapine levels were therapeutic at 451 ng/mL and 312 ng/mL, respectively. Eleven days into the hospital admission, the patient had a surveillance COVID-19 PCR test due to exposure, which returned as positive. He did not display any symptoms of COVID-19 at that time or throughout expected disease course. On the day of positive PCR test, the patient's ANC dropped from 2.2/L (3 days prior) to 1.4/L. On day 13 of admission, ANC dropped further to 0.8/L. This decrease was reported to REMS, and ANC monitoring was increased to daily labs. The clozapine regimen was held for 1 day (3 total doses) and then restarted at the same prior dose, once ANC had increased to 3.2/L the following day. During the weeks following COVID-19 diagnosis, ANC levels were monitored (Table) and adjustments to the schedule of lab draws were made. Despite positive COVID diagnosis, the patient remained asymptomatic and hence was not admitted medically from the ED. He was referred to inpatient psychiatric facilities but declined because the main issues were behavioral disturbances

secondary to underlying IDD. He remained in the ED for his entire treatment awaiting an appropriate disposition plan in collaboration with his guardian and community team.

The patient was also taking other medications that could have contributed to the neutropenia, including fluvoxamine, levetiracetam, oxcarbazepine, and perphenazine. When the ANC fell below 1.5/L, the inpatient hematology team was consulted, which did not have any specific recommendations. The treatment team and the patient's guardian made the decision to discontinue the patient's levetiracetam and fluvoxamine because both of these agents have the potential to affect neutrophil count. This was done after the patient's guardian confirmed he had been seizure-free for 4 years and the patient was still on another antiepileptic agent, oxcarbazepine. Following discontinuation of these agents, no significant clinical changes were noticed in the patient, and therefore a follow-up clozapine level was not drawn.

On hospital day 37, an ANC level of 1.7/L led to monitoring being extended to weekly labs (Table). On hospital day 50, two weeks following the last lab schedule adjustment, the patient's ANC was still above 1.5/L. Throughout the patient's hospital stay ANC levels were monitored and reported to the REMS program with no further drops in ANC found. Because of complex psychosocial circumstances, patient remained in the ED for 60 days prior to being discharged to a new alternative to family living facility.

Discussion

COVID-19 diagnoses have led to several hematologic side effects in patients. The most common reported effects include leukopenia, lymphocytopenia, and elevated D-dimer levels. The infection causes a state of multiple inflammatory reactions within the body. Specifically, the SARS-CoV-2 virus has been shown to activate neutrophil degranulation.⁵ This, along with the unknown mechanism of clozapine inducing neutropenia, could put the patient at a greater risk of experiencing clinically significant neutropenia.

There have been limited reports of patients on clozapine experiencing neutropenia following COVID-19. A European retrospective case series published in 2020 found that ANC levels significantly dropped around the time that the patients tested positive for COVID-19. This case series included 10 individuals who had been on clozapine for a mean of 726 days. The dosing regimens ranged from 200 to 600 mg daily. Around the time of a positive polymerase chain reaction test, all the patient's ANC levels began to drop. Eventually, after the resolution of COVID-19, the patient's ANC levels increased back to their baseline level.⁵

While assessing the patient's moderate neutropenia, the treatment team tried to identify other potential causes.

TABLE: ANC monitoring

Hospital Day	ANC Level	Changes in Clozapine Monitoring
0	2.6/L	ANC level monthly
7	2.2/L	
11	1.4/L	ANC level 3 times weekly
12	1.0/L	
13	0.8/L	HELD and check daily
14	3.2/L	ANC level weekly
15	1.2/L	ANC level 3 times weekly
17	1.6/L	ANC level weekly
19	1.5/L	ANC level weekly (although drawn early to be cautious)
20	2.0/L	ANC level weekly (although drawn early to be cautious)
25	2.6/L	ANC level weekly (although drawn early to be cautious)
27	2.0/L	ANC level weekly (although drawn early to be cautious)
34	1.3/L	ANC level 3 times weekly
37	1.7/L	ANC level weekly
45	1.6/L	ANC level weekly (although drawn early to be cautious)
52	1.8/L	ANC level weekly
59	1.8/L	ANC level weekly

Based on clinical judgment, they held some other medications that could have contributed. Despite the potential for contribution to neutropenia, clinical suspicion was low that medications were the primary cause of decreased ANC. Patients who have recently started a new clozapine regimen are at the highest risk of neutropenia within the first 6 months of initiation. This risk is high through the patient's first year of therapy as dose adjustments are being made.⁶ This patient had been on a stable clozapine regimen for more than 2 years; therefore, the treatment team did not feel that his clozapine regimen was the primary cause of neutropenia. The patient also did not have any known genetic conditions that could have caused neutropenia. The only recent event that occurred at the time of ANC decline was the diagnosis of COVID-19.

Conclusion

This is one of a few available reports highlighting the role that COVID-19 may play in causing neutropenia in stable clozapine patients. COVID-19 can cause complications for many patients, specifically with ones who had been stable on clozapine and can decompensate in their illness if regimen is affected. This case report highlights the importance of strict

monitoring and follow up of ANC levels in patients taking clozapine who have been diagnosed with COVID-19.

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