Clozapine Toxicity Following COVID-19 Infection: A Case Series

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Background

- Clozapine, an atypical antipsychotic, is a very effective medication that has been approved for use in treatment-resistant schizophrenia.
- Clozapine remains an underutilized medication because of its side effect profile and the need for routine laboratory monitoring due to the risk of agranulocytosis (1).
- Clozapine is metabolized in the liver by the cytochrome P450 (CPY450) superfamily of enzymes, mainly CYP1A2 (2).
- Various factors can affect clozapine levels, including concomitant use of CYP450 inhibitors, smoking cessation, and severe respiratory infections. (1,3).
- COVID-19 is a novel coronavirus which emerged in December 2019 and manifests with a broad spectrum of symptoms typically correlating with host inflammatory response. (4).
- Symptoms can range from mild respiratory symptoms to sepsis and even multiple organ failure and can result in substantial hepatic impairment, especially in critical cases (5).
- Cytokines such as interleukin 1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), interferon-α (IFN-α), and IFN-γ which are increased during COVID-19 infection and can impact liver function (6,7).
- We present two cases in clozapine toxicity emerged following COVID-19 infection, and review the mechanism by which this could have occurred.

Case 1

70 year old female with a history of schizophrenia, heart block, and recurrent UTI stable for many years on a regimen of clozapine 150 mg QAM and 200 mg QHS, haloperidol 15 mg QAM and 25 mg QHS, benztropine 1 mg BID, and trazodone 50 mg QHS was admitted to the hospital on 4/27/20 with COVID-19 infection.

Psych was consulted on 4/28/20 for altered mental status and decreased haloperidol dose. Symptomatic stability was achieved after several days, however, on 5/19/20 the patient was again noted to be demonstrating symptoms concerning for psychosis and was placed on civil commitment. On 5/20/20 haloperidol was increased, a clozapine level was ordered, and trazodone was discontinued to avoid polypharmacy. Clozapine level was found to be elevated (Table 1), however, given concern for a non-trough level, and continued psychosis, the dose was not lowered. Psychosis appeared to have improved on 5/22/20, but constipation and eosinophilia were noted. Benztropine was discontinued to reduce the anticholinergic burden, but her status continued to deteriorate, with the emergence of worsening lethargy, sialorrhea, and thrombocytopenia.

A repeat clozapine level was drawn on 5/27/20, returning markedly elevated (Table 1), confirming clozapine toxicity. Clozapine and haloperidol doses were reduced, and the former was ultimately discontinued.

After discontinuation, the patient's mental status continuously improved over the next several days and repeat clozapine levels trended down. Of note, haloperidol level drawn on 6/3/20 returned somewhat elevated, and her dose was decreased. Ultimately she improved to the point where her commitment was lifted, and she was discharged back to her group home on 6/18/20.

Date	Clozapine (ng/mL)	Norclozapine (ng/mL)	Total (ng/mL)
Case 1			
5/20/20*	750	407	1187
5/27/20	1510	603	2113
6/1/20	792	409	1201
6/4/20	171	133	304
6/9/20	<25	27	X
Case 2			
1/24/22	1690	332	2022
1/28/22	1630	376	2006
2/2/22	493	165	658
2/7/22	363	110	473

*level drawn 2 hrs after clozapine ingestion

Clozapine ref range (350-600 ng/ mL)

Table 1: Drawn clozapine levels in both cases, prompted by signs concerning for toxicity. In both case, the patients had been stable on a consistent dose of clozapine for several years. Subsequent levels drawn in tandem with clozapine dose reduction show a return to normal levels. In case 1, the patient was ultimately transitioned to haloperidol monotherapy, hence clozapine levels reducing to undetectable levels

Case 2

65 year old female with a history of schizoaffective disorder, bipolar type, type 2 diabetes, hypothyroidism, seizure disorder, and recently-recovered COVID-19 infection stable on a regimen of clozapine 200 mg BID, benztropine 0.5 mg daily, and valproic acid 1000 mg QHS was admitted to the hospital on 1/23/22 for altered mental status and fall after having been discharged the day prior at her psychiatric baseline.

Psych was consulted on 1/23/22, and found the patient to be demonstrating echolalia and appearing to respond to internal stimuli. A clozapine level was ordered (Table 1), and returned elevated.

When seen on 1/27/22, the patient was noted to have deteriorated, presenting with lethargy and myoclonic jerking in her right upper extremity. Her dose of clozapine was decreased to 100 mg BID, after which a repeat level was drawn. Repeat level returned elevated, but slightly lower, and when the patient was seen on 2/1/22, she presented as significantly more alert, with resolution of myoclonus and no overt psychosis.

Given lack of eosinophilia or thrombocytopenia, clozapine dose was maintained at 100 mg BID, and her clozapine level was trended, showing a return to a therapeutic level. She remained at her psychiatric baseline and was discharged to a skilled nursing facility on 2/9/22.

Discussion

Despite being on the market for several decades, clozapine remains one of the most effective antipsychotic medications, especially for management for treatment-resistant schizophrenia. As such, it is often used in some of our sickest patients, but is not without its drawbacks. In addition to the potential for agranulocytosis, clozapine can also accumulate to toxic levels resulting in an anticholinergic syndrome with a change in consciousness, tachycardia, respiratory depression, and sialorrhea. Because of this, it is important to monitor both neutrophil counts and clozapine levels in these patients. Although most patients rarely experience unprompted toxicity following stabilization on a dose of clozapine, the two cases presented emphasize the impact that inflammatory illness can have on this vulnerable patient population.

It is known that inflammatory processes can affect clozapine clearance which is hypothesized to have occurred in the patients described above. Clozapine is metabolized primarily by CYP1A2, the activity of which has been proposed as a potential determinant of clozapine dose requirements (2). COVID-19 has been previously shown to be associated with liver injury in some patients, with more severe disease being associated with dysregulation of liver biomarkers (5). It is also been indicated in the literature that CYP1A2 is downregulated up to 53% during active COVID-19 infection (4). Taken together, it appears quite likely that severe COVID-19 infection can result in hepatic inflammation, leading to significant CYP1A2 downregulation. This leads to the liver being unable to effectively metabolize doses of clozapine that patients had previously tolerated, sometimes for many years.

These cases serve as an important reminder that, although respiratory symptoms of COVID-19 are most apparent to the public eye, the virus has potential to affect many systems, both directly and indirectly. Patients who are prescribed clozapine typically suffer from treatment-resistant schizophrenia and are an especially vulnerable part of our treated population in terms of daily functioning and self-advocacy. As patients with COVID-19 are often admitted to medical floors, this serves to underscore the importance of coordinated care and cross-education between both medicine and psychiatric services. We must be diligent in monitoring their care and recognizing symptoms of toxicity, especially as COVID-19 seems to be here to stay.

References

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