Proactive Modification to Clozapine Dose in a Patient With Pneumonia to Prevent Toxicity

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Fast action is required to protect clozapine patients who have pneumonia. Patients treated with clozapine may have a higher likelihood of developing pneumonia than patients treated with other antipsychotics or the general public.[1] This risk very likely comes from common clozapine side effects like sedation, dysphagia, and hypersalivation and is elevated by the emergence of toxic blood clozapine levels found in the setting of pneumonia and other infections.[2] A review of the World Health Organization (WHO) global database containing greater than 20 million spontaneously reported adverse drug reactions (ADRs) from 134 countries reveals pneumonia as the most frequently reported clozapine-related ADR with fatal outcome.[3]

Case Report

A 57-year-old white male nonsmoker with a history of treatment-resistant schizophrenia (*DSM-5*), Parkinson's disease (*ICD-10-CM*), hypothyroidism, and insomnia developed flu-like symptoms (day 151 of clozapine treatment) while admitted to a psychiatric hospital. Current daily dose of clozapine (600 mg) was empirically reduced to 500 mg orally at bedtime (clozapine day 153) due to concerns that the patient could be developing pneumonia despite normal breath sounds bilaterally. Later that night, the patient's condition rapidly declined over a few hours with high fever (maximum = 104.6 °F), difficulty breathing, dropping O_2 saturation (85% on room air), lethargy, and cough and was transferred for medical evaluation. Pneumonia was confirmed by chest x-ray, and the patient was admitted for intravenous antibiotics and supportive care. At this time, serum C-reactive protein (CRP) level was found to be 12.2 mg/dL, and serum clozapine level was drawn and sent out; there was a significant time delay for clozapine level results since this assay is not done on site, so the decision was made to hold clozapine for 2 days. Clozapine was then restarted at a lower dose (100 mg/d), which was escalated as the patient improved and CRP level normalized. The patient was substantially improved after 48 hours and was discharged to return to the psychiatric hospital after 4 days; he remained psychiatrically stable throughout. Eventually, the serum clozapine level results were obtained and showed that the initial clozapine level from first day of pneumonia hospitalization (ie, clozapine day 153) was 1,695 ng/mL, which was about 3 times the usual level for this patient (see Table 1 for a summary of clozapine dosing, therapeutic drug monitoring, and CRP levels for this patient).

Discussion

Immediate action is needed to reduce risk associated with clozapine toxicity in an already compromised patient, especially in light of the coronavirus disease 2019 (COVID-19) pandemic. A patient taking clozapine who presents with pneumonia (or other serious infection) and elevated CRP level should warrant clozapine dose reduction or temporary cessation of clozapine treatment.[4] It is not necessary to wait for results of blood clozapine level testing. Given the reciprocity between pneumonia and increased serum clozapine levels,[2] it is important to increase awareness across the health care spectrum. Some clinicians[5] suggest reducing clozapine doses by 50% in the setting of pneumonia; others[2] advise a gradual dose reduction. In this case, initially stopping clozapine treatment was warranted given the severity of illness. Clinical impact of clozapine toxicity can include oversedation and delirium, as well

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Table 1. Clozapine Dosing, Therapeutic Drug Monitoring (TDM), and Inflammatory Marker in a Patient With Pneumonia

Clozapine Treatment Day[a]	Clozapine Dose (mg/d)	TDM Blood Level (ng/mL)			C/D Ratio[c]	CRP (mg/dL)[d]
		Clozapine[b]	Norclozapine	Total		
110	600	603	191	794	1.3	…
139	600	645	217	862	1.4	…
153	500	1,695	457	2,152	4.3	12.2
160	200	169	Unknown[e]	169	0.8	2.1

[a]Concomitant medications throughout included the following: carbidopa 25 mg/levodopa 100 mg × 4 tablets/d, divalproex sodium 2,500 mg/d, ferrous sulfate 650 mg/d, levothyroxine 50 µg/d, melatonin 10 mg/d, PEG 3350 17 g/d, and sennosides 34.4 mg with docusate 200 mg/d.
[b]Reference range, 350–700 mg/mL
[c]Concentration-to-dose (C/D) ratio is the total of parent plus metabolite divided by the clozapine daily dose; use of parent plus metabolite in C/D ratio calculation better estimates clearance and impact on side effects.[4]
[d]Normal limit is < 0.9 mg/dL.
[e]Minimum detection of laboratory used for norclozapine is 100 ng/mL; the norclozapine level was below detectable level on this date.
Abbreviations: CRP = C-reactive protein, PEG = polyethylene glycol.

as neutropenia, myocarditis, and seizure, all of which can contribute to poor outcomes for clozapine-treated patients with pneumonia.

Clozapine is arguably the most effective antipsychotic available for the treatment of schizophrenia; however, it has higher risk and requires specialization when prescribed. Practitioners outside of psychiatry are generally unfamiliar with the nuances of managing clozapine therapy, so consultation with a psychiatrist or psychiatric pharmacist would be valuable. It is important to retain a patient's ability to continue clozapine therapy, as it provides overall significant reductions in morbidity and mortality compared to treatment with other antipsychotics or to no treatment of schizophrenia.[6]

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