Clozapine Intoxication in COVID-19

Niels Tio, M.D., Peter F.J. Schulte, M.D., Ph.D., Harrie J.M. Martens, Pharm.D.

Mr. A, a 46-year-old Caucasian nonsmoker, lives at an institution for people with intellectual disabilities. He is known to have a severe intellectual disability of unknown cause as well as schizophrenia, for which he takes 200 mg of clozapine twice daily. The clozapine trough level at steady state was 553 μg/L, the clozapine level/dose (C/D) ratio 1.4, and the clozapine/norclozapine (C/N) ratio 1.7 (Table 1).

Mr. A's past medical history records several infections, including one episode of bacterial pneumonia, two of bronchitis, and an infection of the upper respiratory tract, not described in further detail (see Table 1). With the bronchitis episodes and the upper respiratory tract infection, the clozapine level did not rise further than 661 μg/L (C/D ratio, 1.7). With the bacterial pneumonia, the level rose to 1,183 μg/L (C/D ratio, 2.4). On several occasions, including during the bacterial pneumonia, halving the dosage of clozapine led to psychotic decompensation. On the basis of these clinical experiences, it was concluded that for this patient the dosage of clozapine could not be automatically halved when signs of inflammation appeared, given that in several cases respiratory tract infections had not resulted in a doubling of clozapine levels and halving the dosage resulted in lower, evidently subtherapeutic levels.

In April 2020, during the COVID-19 pandemic, Mr. A was found to have sonorous wheezes, audible without stethoscope, but no further clinical symptoms or abnormal test results (see Table 1 for the progression of the case). When COVID-19 was suspected (day 1), isolation measures were taken, a nasopharyngeal swab was collected, and a blood test was conducted. The clozapine level was in accordance with baseline. The rest of the blood tests showed no abnormalities, but the nasopharyngeal swab tested positive for COVID-19.

From day 4 onward, Mr. A became increasingly ill. He was sweating and his face was pale, with blue lips. His temperature rose to 38.4°C. He also showed possible signs of clozapine intoxication, namely, ataxia and tremors. He was given oxygen and paracetamol. Given his history of psychotic decompensation after his clozapine dosage was halved during fever, from day 4 onward the dose given depended on whether his temperature was ≥38°C. If it was, the dosage was reduced to 300 mg per day (days 4, 5, and 7); on day 6 the dosage went back to 400 mg/day (the patient's normal daily dose). During days 4 to 6, Mr. A seemed lethargic, with sweating, echolalia, and reduced initiative. His temperature fluctuated between 37.1 and 38.7°C. On day 7, the patient's condition deteriorated further, with a temperature of 39.4°C. On auscultation, crackles could be heard at the base of the right lung. Because bacterial pneumonia was suspected in addition to COVID-19, the patient was given amoxicillin/clavulanic acid 500/125 mg t.i.d. for 7 days and the blood tests were repeated. His co-medication in this period was atenolol, diazepam, esomeprazole, and lithium. The clozapine trough level turned out to be three times as high as usual: 1,814 μg/L. Because this was not a steady-state situation, a C/D ratio of 5 was calculated using the mean dosage over the past 5 days. The C/N ratio was 3.5. At this point clozapine was stopped altogether. From day 9 onward, the patient began to recover. At that point the clozapine level was 1,335 μg/L. From day 10 onward, after the clozapine had been discontinued for 48 hours, the clozapine dosage was cautiously increased again. On day 13, the clozapine level was 213 μg/L (dosage, 50 mg/day), and on day 19, 107 μg/L (dosage 100 mg/day). On days 30 and 37, the serum clozapine levels were normal, as were the C/D and C/N ratios; the patient had clinically recovered and the clozapine dosage had now been increased to 350 mg/day (Figure 1).

Clozapine is regarded as a very effective antipsychotic (1). For efficacy in schizophrenia, an expert guideline recommends trough steady-state clozapine concentrations of 350–600 μg/L (2).

It is well known that an inflammatory response associated with respiratory tract infections may cause increased clozapine serum levels, leading to symptoms of clozapine intoxication such as sedation and lethargy, sialorrhea, ataxia, convulsions, and ECG abnormalities (3–5). Infections cause relevant increases in clozapine levels only when there are systemic manifestations of fever with C-reactive protein (CRP) elevations and a significant cytokine release (6). Mild respiratory infections without fever or leukocytosis usually cause minimal elevations.

Clozapine is primarily metabolized in the liver via the cytochrome P450 system (7, 8). About 70% is metabolized to norclozapine by CYP1A2. With inflammation, cytokines are increased, and interleukin 1β (IL-1β), IL-6, tumor necrosis

TABLE 1. Past history and case history of a patient on clozapine before and during a COVID-19 infection

Year or Day	Clinical	O_2 Sat.	Respiratory Rate (min)	Temperature (°C)	CRP (mg/L)	WBC ($\times 10^9$ cells/L)
Past history (through April 2020)						
2013	Bronchitis			36		
2018	Pneumonia			37	22	
2019	Bronchitis			37		
2019	Pneumonia			38.1	47	
2020	Upper respiratory tract infection			37.6	39	
Current case (April 2020)						
Baseline[e]						9
1	Sonorous wheezes audible without stethoscope. Nasopharyngeal swab, PCR SARS-coronavirus-2 RNA: positive	95%–96%	14	36.9		
2	Sedimentation rate, 2 mm/hour			37.0–37.5	9	5.3
4	Tremors in arms and legs, unsteady on feet, sweating, pale face, blue lips			38.4		
5	Clinical deterioration, loss of initiative, echolalia		24	38.7	13	
6	Clinical deterioration, increased fatigue	93%	24	37.1–38.1		
7	Lungs: vesicular breath sounds, dubious basal right crackles. Gross tremors in arms and hands. Clinical deterioration. Working diagnosis: bacterial pneumonia in addition to COVID-19	90%–96%		39.4	Unknown (test failed)	6
8	Clinical deterioration, increased fatigue	98%	20			
9	Clinical improvement: more active	95%	20	38.4		2.1
10	Clinical improvement	95%–98%		37.6–38.0		
11	Clinical improvement	93%–99%	16	36.7–38.1		
12	Clinical deterioration: fatigue, reduced alertness	95%–97%	20	37.3		
13	Clinical deterioration: fatigue, dyspnea, drowsy	88%–99%	14	35.2		3.1
14	Clinical improvement, but tired		18	37.8		
15	Clinical improvement	97%	16	36.3		
16	Clinical improvement	98%	14	36.9		
17, 18	Clinical improvement					
19	Clinical improvement	95%–98%	18	36.3		10
20	Clinical improvement	99%		36.1		
23	Clinical improvement					6.8
30	Clinically recovered					7.4
37	Clinically recovered					6.7

[a]Divided over two doses per day (8 a.m., 8 p.m.).
[b]Trough level, 12 hours after night dose and before morning dose, except on day 9, when clozapine had been stopped for 24 hours.
[c]Ratio of clozapine level to clozapine dosage. A steady state for the clozapine level is required for the calculation. If this was absent, the mean dosage over the preceding 5 days was used (days 7 and 19).
[d]Ratio of clozapine level to norclozapine level.
[e]Sixteen days before day 1 of COVID-19 progression.

factor-α (TNF-α), interferon-α (IFN-α), and IFN-γ in particular seem to inhibit the activity of CYP1A2 (3, 7, 9). This results in an increase in the clozapine level. However, symptoms of intoxication are not observed in all cases of high clozapine levels. A possible explanation of this is that in plasma, 95% of clozapine is bound to the acute-phase protein alpha-1-acid glycoprotein (AGP), the concentration of which rises during an inflammatory response. It is thought that an increase in AGP leads to an elevation in the protein-bound concentration of clozapine, while the unbound concentration seems to be less affected (10). The AGP concentrations and the degree of increase during an infection vary depending on the individual and the situation (11).

Other factors that can cause a reduction in the metabolic activity of CYP1A2 are cessation of smoking or of inducing drugs and coadministration of CYP1A2-inhibiting drugs, including caffeine (12). All these factors were unchanged or absent in Mr. A.

The degree of increase in the clozapine level associated with inflammation varies across cases. The literature identifies a median clozapine level increase of 48% in inflammation (CRP ≥5 mg/L) (5). Based on this, it is recommended that if there are any signs of inflammation, the clozapine dosage

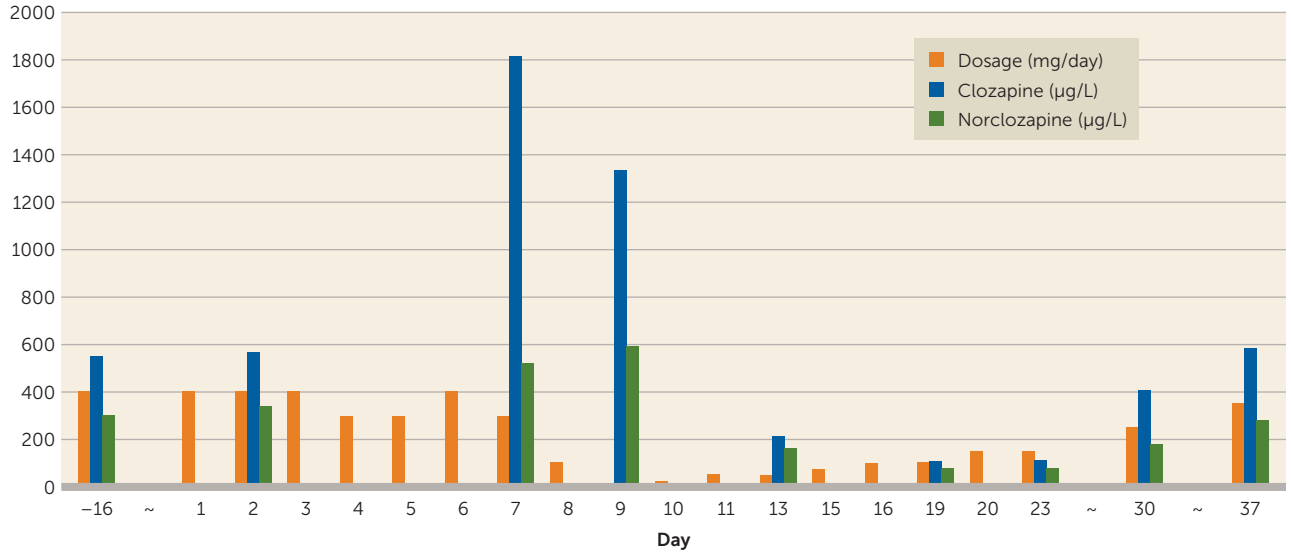
Neutrophils ($\times 10^9$ cells/L)	Clozapine dosage (mg/day)[a]	Clozapine level (ng/mL)[b]	Norclozapine level (ng/mL)[b]	C/D[c]	C/N[d]	Treatment Strategy
	300	210	?	0.7	?	
	500	1,183	490	2.4	2.4	
	240	264	170	1.1	1.5	
	450	817	350	1.8	2.3	
	400	661	380	1.7	1.7	
6.4	400	553	300	1.4	1.8	
	400					Home quarantine
4.2	400	565	340	1.4	1.7	
	300					Halve clozapine dosage per dose at temperatures ≥38°C. Start oxygen 1 liter/minute, start paracetamol 1,000 mg t.i.d.
	300					Increase oxygen to 2 liters/minute
	400					Increase oxygen to 3 liters/minute
5.2	300	1,814	520	5.0	3.5	Increase oxygen to 4 liters/minute. Start amoxicillin/clavulanic acid 500/125 mg t.i.d. for 7 days
	100					
1.3	0	1,335	590		2.2	Reduce oxygen to 3 liters/minute
	25					
	50					
	50					
1.8	50	213	160		1.3	
	50					Reduce oxygen to 2 liters/minute
	75					
	100					Reduce oxygen to 1 liter/minute
	100					
7.5	100	107	80	1.4	1.3	No extra oxygen
	150					Stop extra oxygen. Continue home quarantine in accordance with guidelines. Clozapine titration schedule to usual dose of 400 mg/day, in accordance with Clozapine Plus Werkgroep guideline
4.2	150	112	80	1.1	1.4	
5.2	250	406	180	1.6	2.7	
4.3	350	583	280	1.7	2.0	

should be halved and clozapine levels monitored (5). However, some patients with infections have normal levels, whereas in others the levels more than triple (3, 4). In our patient's case, the clozapine level more than tripled in the presence of pneumonia and COVID-19. On this occasion, the level was considerably higher than with previous respiratory tract infections. Unfortunately, measurement of CRP failed during this episode, so the degree of inflammation cannot be compared with that in earlier episodes of respiratory tract infection in this patient.

The C/D ratio is a measure of clozapine clearance. For a reliable interpretation, a steady state is necessary. With changing clozapine dosages, the mean dosage over the 5 days before blood sampling has been proposed as an acceptable basis for calculating the C/D ratio (6). Because steady-state levels were not possible during infection, we used mean dosage levels calculated over the preceding 5 days (day 7 and day 19). A very low C/D ratio indicates a rapid metabolizer, while a very high C/D ratio indicates a poor metabolizer (average ranges, Caucasians, 0.6–1.2; Chinese, 1.2–2.4) (6–13). The C/D ratio at a steady state may help to assess whether and by how much the dosage should be reduced if a baseline C/D ratio is known. For this purpose, the current clozapine dosage is multiplied by the baseline C/D ratio and divided by the actual C/D ratio. This is the dosage for reaching the new steady state baseline level again. However, if the level is much higher or there are clinical symptoms of intoxication, clozapine treatment must first be temporarily suspended so that the concentration falls back to the desired level. It is advisable to wait at least until any symptoms of intoxication have clinically disappeared (4).

In Mr. A, an increase in the C/N ratio was also observed, which may indicate an inhibition of CYP1A2 (14) (see Table 1). However, a recent review found no evidence that the C/N ratio is a measure of CYP1A2 activity (13).

FIGURE 1. Clozapine dosage and serum levels of clozapine and norclozapine in a patient before and during a COVID-19 infection



In this patient, we found a greater increase in the clozapine level with this respiratory tract infection than with previous respiratory tract infections. An increase in cytokines, including IL-1β, IL-6 and TNF-α, in COVID-19 has been reported, and this increase may develop into cytokine storm syndrome (15). The degree of cytokine increase correlates with the severity of the illness and the prognosis. SARS-CoV is accompanied by a greater cytokine increase than other viral infections, such as influenza and respiratory syncytial virus (16). In bacterial pneumonia, a cytokine storm is rare. This may explain why Mr. A's clozapine level rose considerably more than with previous respiratory tract infections. The progression of his illness suggests that a COVID-19 infection may cause an extreme elevation in clozapine levels. If this is the case, halving the clozapine dosage in COVID-19 in accordance with the recent recommendation (17) will not be sufficient.

In summary, COVID-19 may be associated with hyperinflammation and extremely severe pneumonia. Our case illustrates that this can lead to an unexpectedly high increase in the clozapine level, with the danger of intoxication. The recommendation to reduce the dosage of clozapine by half is therefore probably not cautious enough. Frequent monitoring of the patient for any symptoms of intoxication and monitoring the clozapine levels may help to determine the dose day by day to avoid both underdosing, with the risk of psychotic relapse, and overdosing, with the risk of intoxication. Calculating the C/D ratio may help with this.

AUTHOR AND ARTICLE INFORMATION

Stichting SBOH and Stichting Ipse de Bruggen, Nieuwveen, the Netherlands (Tio); Mental Health Services Noord-Holland-Noord, Alkmaar, the Netherlands (Schulte); Noordwest Hospital, Alkmaar, the Netherlands (Martens).

Send correspondence to Dr. Tio (niels.tio@ipsedebruggen.nl).

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