Elevated clozapine levels in patients with COVID-19 infection

Martí-Bonany J, Pérez Sánchez E, Pérez Carre M, Martínez Casamitjana MI, Fortuny Olive JR, Macias Castellví C, Carrió Diez E, Lana Moliner F, Sánchez González R.

Institut de Neuropsiquiatria i Addiccions, Centre Emili Mira, Parc de Salut Mar, Barcelona.

INTRODUCTION

Clozapine is the most effective antipsychotic for treatment resistant schizophrenia. The COVID-19 pandemic presents a variety of unique challenges for psychiatric practice. In patients treated with clozapine, COVID-19 infection may result in complications including an increased risk of pneumonia, clozapine toxicity, and disruption to clozapine treatment by COVID-19 induced lymphopenia.

OBJECTIVES

We report 5 cases of elevated clozapine levels occurring in patients with COVID-19 infection who had been previously managed for several years on stable doses.

METHODS

Subjects: 48 Patients diagnosed with severe mental disorder admitted to a long-stay psychiatric unit.
COVID-19 infection confirmed by positive nasopharyngeal swab for viral ribonucleic acid of SARS-CoV-2.
Hematological controls between March and April 2020.

CONCLUSIONS

- These cases serve as a reminder to clinicans that clozapine is associated with a wide range of medical complications and toxicities that complicate the management of COVID-19.
- Covid-19 infection is associated with increased serum clozapine levels by probably multifactorial mechanisms (systemic infection, reduced smoking).
- Importance of full clinical assessment of suspected COVID-19 infection in clozapine treated patients, including assessment clozapine level, and full blood count.
- The general recommendation is to reduce the dose of clozapine. Once fever and/or pneumonia develops, the clozapine dose should be cut in half to decrease the risk of clozapine intoxication

RESULTS

Table 1 shows the sample characteristics of the admitted patients. 16 (33%) receiving clozapine treatment. There were 18 (37.5%) cases with covid-19 infection. Clozapine-treated patients with covid-19 infection were 5 (10.4%)
Table 2 shows the results of clozapine-treated patients with covid-19 infection.
Increases in plasma clozapine levels were observed in all cases (49'38 to 307.5%). The evolution of clozapine plasma levels is shown in figure 1.
We don't have the clozapine levels of a patient who presented a pneumonia requiring admission and treatment in the general hospital.
Two cases of neutropenia were observed, of which one had to discontinue treatment with clozapine.
In the other three patients the dose of clozapine was reduced and they did not present haematological or intoxication complications that required further adjustments.

Table 1 Sample characteristics of admitted patients

	COVID-19 +	COVID-19 -	TOTAL
CLOZAPINE	5 (10'4%)	11 (22'9%)	16 (33'3%)
NON-CLOZAPINE	13 (27'1%)	19 (39'6%)	32 (66'7%)
TOTAL	18 (37'5%)	30 (62'5%)	48 (100%)

Figure 1. Evolution of clozapine plasma levels in covid-19 positive patients.

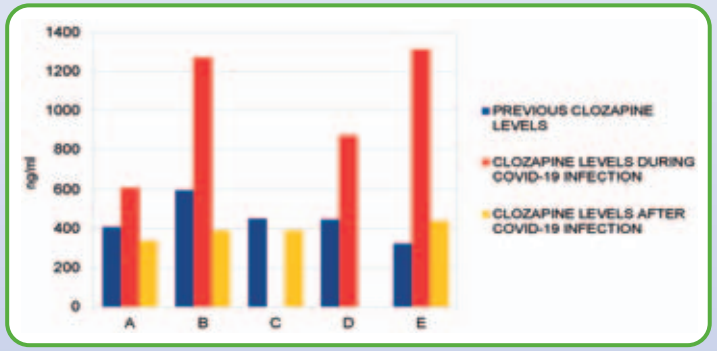

Table 2. Clozapine-treated patients with covid-19 infection.

Patients	Previous clozapine levels *	Clozapine levels during covid-19 infection *	Increase	Neutropenia	Action	Clozapine levels after covid-19 infection *
A	407 ng/ml (300 mg/d)	608 ng/ml (300 mg/d)	49'38%	NO	reduce clozapine (225mg/d)	338'1 ng/ml (225 mg/d)
B	596 ng/ml (400 mg/d)	1270 ng/ml (400 mg/d)	113,00%	NO	reduce clozapine (300mg/d)	390 ng/ml (300 mg/d)
C	450 ng/ml (300 mg/d)	NO	NO	YES	Pneumonia tretated in General Hospital	529 ng/ml (300 mg/d)
D	445 ng/ml (300 mg/d)	870 ng/ml (300 mg/d)	95'5%	YES	withdrawal clozapine	NO
E	322 ng/ml (400 mg/d)	1312 ng/ml (400 mg/d)	307'5%	NO	reduce clozapine (300mg/d)	438'8 ng/ml (300 mg/d)

* clozapine plasma levels in ng/ml and total oral clozapine in mg per day.

REFERENCES

Leon J de, Ruan C-J, Verdoux H, Wang C. Clozapine is strongly associated with the risk of pneumonia and inflammation. General Psychiatry. 2020;33(2):e100183. doi:10.1136/gpsych-2019-100183
Cranshaw T, Harikumar T.COVID-19 Infection May Cause Clozapine Intoxication: Case Report and Discussion.Schizophr Bull. 2020 Jul 8;46(4):751. doi: 10.1093/schbul/sbaa070.
Siskind D, Honer WG, Clark S et al.Consensus statement on the use of clozapine during the COVID-19 pandemic. J Psychiatry Neurosci. 2020 Apr 3;45(4):200061. doi: 10.1503/jpn.200061.
Dotson S, Hartvigsen N, Wesner T, et al. Clozapine Toxicity in the Setting of COVID-19. Psychosomatics. 2020 Sep-Oct;61(5):577-578. doi: 10.1016/j.psym.2020.05.025.