Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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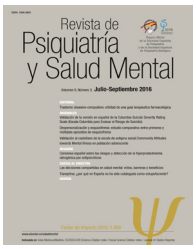

LETTER TO THE EDITOR

A Covid-19 outbreak in a Spanish long-term psychiatric hospital led to infections in 6 clozapine patients: elevations in their plasma clozapine levels

Un brote por Covid-19 en un hospital psiquiátrico de larga estancia español dio lugar a infecciones en 6 pacientes en tratamiento con clozapina: elevaciones en los niveles plasmáticos de clozapina

Dear Editor,

Clozapine is mainly metabolized by the cytochrome P450 1A2 (CYP1A2) leading to its main metabolite, norclozapine.[1] Clozapine metabolism is influenced by 3 levels of complexity: (1) ancestry groups, (2) sex-smoking subgroups and (3) presence/absence of poor metabolizer (PM) status.[2] The concentration providing 350 ng/ml, the minimum therapeutic dose, can be used to compare ancestry groups and patients.[1–3] Asians and their descendants, Amerindians, need lower doses than Europeans.[3] In European patients the minimum therapeutic dose is 250 mg/day for female non-smokers and 400 mg/day for male smokers. PMs usually have around half the ability to metabolize clozapine, requiring half the dose.[2] Non-genetic CYP1A2 PMs are probably much more frequent than genetic PMs and can be explained by use of CYP1A2 inhibitors, obesity or inflammation. Any systemic inflammation (whether or not associated with infection) releases cytokines and increases the C-reactive protein (CRP) inhibiting CYP1A2.[1]

In a large clozapine cohort of 131 Chinese inpatients, 18 different episodes of infection/inflammation were associated with: (1) lack of clinically relevant effects in 11% of the infection episodes (no leukocytosis or ↑ CRP), (2) required reduction of the clozapine dose to one-half to compensate for elevated levels (61% of the infection episodes), and (3) required reduction of the clozapine dose to one-third to compensate for elevated levels (28% of infection episodes).[4]

An expert consensus statement on Covid-19 described the risk of clozapine intoxication during severe infections and proposed halving the dose to avoid intoxication.[5] In a comprehensive review, Veerman et al.[6] identified 8 cases of patients with elevated clozapine levels during Covid-19 infections and 4 deaths. It is possible the cases reviewed by Veerman et al.[6] did not include mild cases. According to the Beijing study in other infections, mild infections with no CRP elevations may have no effects on clozapine levels. Transient drops in neutrophil count during Covid-19 infections have been described.[7]

This is a systematic study of clozapine level elevations during a Covid-19 outbreak at a Spanish psychiatric hospital with long-term admissions including all severity levels of the Covid-19 infection. As the patients had been followed by obtaining clozapine levels for years, the treating psychiatrists made decisions about decreasing clozapine doses based on the increase in clozapine levels during the Covid-19 infection.

The Covid-19 pandemic arrived in Spain in March 2020 but the first case in this Spanish long-term psychiatric hospital was on January 11, 2021. During the 5-week outbreak, a total of 1480 Covid-19 tests using polymerase chain reaction (PCR) led to 27 positive cases. This provided an incidence of 15% (27/178). Among the 35 clozapine patients, six of them became positive, providing a slightly higher incidence of 17% (6/35). This report on Covid-19 infections focuses on dosage changes after obtaining clozapine levels and using each of the 6 patients as their own control (Supplementary Tables S1–S6).

Plasma clozapine and norclozapine concentrations were collected in trough and steady-state conditions. Steady state was defined as at least 5 days without any clozapine dosing changes (5 half-lives of 24 h).[1,2] The concentrations were measured with high-performance liquid chromatography (HPLC) using a previously published method.[8] During the Covid-19 outbreak, psychiatrists were aware of the risk of clozapine intoxication during infections; thus a clozapine blood level was collected in any patient who was identified as positive for Covid-19 independently of any symptoms of Covid-19 and/or clozapine intoxication. Due the urgency and possible risk for patients, the laboratory was willing to provide the results of the clozapine levels in 2 days for 5 of 6 cases (and 1 week for Case 3).

The clozapine C/D ratio in ng/ml per mg/day was calculated by dividing the trough serum concentration by the dose. The total clozapine C/D ratio in ng/ml per mg/day was calculated by dividing the total serum concentration (clozapine and norclozapine) by the dose as an additional measure of clozapine clearance.

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Table 1 Description of 6 patients with Covid-19 infections and dose correction factors (6 Supplementary Tables provide details).

Patient number:	Covid-19 symptoms	↑ CRP	Clozapine C/D ratio			Highest C on D	D adjustment
			No	Infection		Total C on D	
Age (yr) sex smoking			Mean	Mean	Peak	(ng/ml on mg/day)	
1:49 ♀ smoker	Mild	No					No
	Fever & little respiratory		0.76	0.72	0.72	255 on 350	
	Symptoms		*N* = 4	*N* = 1	*N* = 1	482 on 350	
2: 61 ♀ non-smoker	Mild	Yes	1.19	3.27	3.40	943 on 300	×0.50
	Fever & dry cough		*N* = 3	*N* = 2	*N* = 1	1462 on 300	
3: 64 ♂ smoker	Asymptomatic	Mild	0.89	1.68	1.93	581 on 300	No
			N = 3	*N* = 2	*N* = 1	911 on 300	
4: 69 ♂	Severe	Very	1.92	3.35	3.35	1006 on 300	×0.67
non-smoker	Pneumonia[a]	high	*N* = 4	*N* = 1	*N* = 1	1535 on 300	
5:	Mild	Mild	2.45	1.81	1.81	360 on 200	No
54	Fever		*N* = 3	*N* = 1	*N* = 1	599 on 200	
6: 37 ♂ smoker	Mild	Mild	0.85	1.36	1.36	409 on 300	No
non-			*N* = 3	*N* = 1	*N* = 1	613 on 300	
smoker	Prior polytrauma[b]			2.24	2.24	896 on 400	
				N = 1	*N* = 1	1233 on 400	

C: concentration; C/D, concentration-to-dose in ng/ml per mg/day; CRP, c-reactive protein; D, dose.

[a] The clinical picture was severe, requiring admission to the Infectious Diseases Department on the tenth day after diagnosis due to high fever with respiratory distress. The patient was diagnosed with left upper lobe pneumonia with hypoxemia and received treatment with ceftriaxone, azithromycin, oxygen therapy and dexamethasone with progressive improvement. After nine days of admission, the patient returned to the psychiatric hospital.

[b] Initially, the patient was admitted to the Intensive Care Unit and received a dose of 400 mg/day. He suffered polytrauma following a fall from a sixth floor. During this period, he was followed by the consultation-liaison psychiatry team who prescribed 400 mg/day with clozapine levels of 896 ng/ml and norclozapine levels of 337 ng/dl at the time of very high CRP (8.93 mg/dl); he was not smoking. The lack of smoking and the inflammation associated with polytrauma decreased his clozapine metabolism. The daily dose of clozapine was reduced from 400 to 300 mg/day. A few weeks later the patient returned to the psychiatric hospital and a few days later was diagnosed with Covid-19.

Table 1 shows that, of the 6 patients, 4 required no dosage changes and 2 had their clozapine dosage reduced. The cases with no dosage change include: Case 1 with mild symptoms and no CRP elevations; Case 3, who was asymptomatic and had a mild CRP elevation; and Cases 5 and 6 with mild symptoms and mild CRP elevations.

Of the two cases with changes, Case 2 had relatively mild symptoms except for systemic inflammation with fever and CRP elevations, so the clozapine dosage was cut in half (from 300 to 150 mg/day) since on 300 mg/day the clozapine levels had increased to 943 ng/ml (total 1462 ng/ml). Case 4 had severe symptoms and very high CRP elevations and required an admission to a medical hospital. The psychiatrist cut the dosage by one-third (from 300 to 200 mg/day) since on 300 mg/day the clozapine levels increased to 1006 ng/ml (total: 1535 ng/ml).

In summary, 66% (4/6) of patients were managed with no dosage changes because the clozapine elevations were mild if present. Dosage corrections occurred in 2 patients, one of which had to be transferred to a medical hospital due to severe pneumonia. Our clozapine prescribers are familiar with the use of CRP and clozapine levels for managing clozapine dosing and have access to prior clozapine levels over the years for all these patients. Similarly, Tio et al.[9] described a clozapine intoxication in a patient followed with clozapine levels for years.

In our sample no patient died. We found a US case report of a patient who died during a Covid-19 infection but levels were not measured,[10] and 3 deaths from among 8 patients with Covid-19 infections from a university hospital in the United Kingdom (UK).[11] In this UK sample, four cases with Covid-19 pneumonia were described in detail in the article: 3 died and no levels were described but, in the patient who survived, two levels were reported.

Our results are limited by their naturalistic nature and may not extrapolate to other settings; our results reflect a long-term psychiatric hospital where patients have been known for many years and a laboratory has been willing to expedite the measures of clozapine levels. Our results suggest that mild Covid-19 infections with mild symptoms and mild CRP elevations can be managed with no dosage reductions, as long as clozapine levels can be measured, promptly received and compared with their baseline. New methods, such as dried blood spot, are simplifying the measuring of clozapine levels.[12] When clozapine levels are not available, it may be important to halve the dose when Covid-19 symptoms are severe, including fever or a dramatic increase in CRP. Similarly, the onset or major exacerbation of some clozapine ADRs, including hypersalivation, constipation, sedation or myoclonus which are dose-dependent side effects, may signal that clozapine levels may be increasing and halving clozapine dose may be indicated.

Authors' contributions

This retrospective review was planned by MAR and JdL. The data was collected by MAR and MRCB. MAR drafted the initial version of the manuscript and JdL rewrote it to fit the style of the journal. All authors reviewed the initial draft and made critical contributions to the interpretation of the data and approved the manuscript.

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Conflict of interest

No commercial organizations had any role in writing this paper for publication. In the past 3 years, the authors had no commercial conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.rpsm.2022.06.001

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