

The effect of COVID-19 on absolute neutrophil counts in patients taking clozapine

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Abstract

Clozapine is associated with haematological side effects, including neutropaenia, which can signal impending life-threatening agranulocytosis. Patients with COVID-19 infection frequently experience lymphopaenia, but not neutropaenia. We present 13 patients established on clozapine who developed COVID-19 infection. There were no significant differences in total white cell or neutrophil counts between pre-COVID-19, intra-COVID-19 or post-COVID-19 periods. We therefore suggest that patients who develop COVID-19 should generally have their clozapine treatment continued. Patients taking clozapine who develop neutropaenia during COVID-19 infection should be investigated and monitored as in normal practice, because changes in neutrophil counts cannot be assumed to be due to the viral infection.

Keywords: clozapine, coronavirus, COVID-19, schizophrenia, agranulocytosis, neutropaenia

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Introduction

Clozapine has known haematological side effects. The most common (2.7% of patients¹) is neutropaenia, which can sometimes portend life-threatening agranulocytosis (0.4% of patients).² For this reason, monitoring of the WCC [including absolute neutrophil count (ANC)] is mandatory in many countries.³ Over 80% of cases of agranulocytosis occur in the first 18 weeks of treatment.⁴ By the end of the first year of treatment, the risk of agranulocytosis is comparable with that of other antipsychotics.⁵ Neutrophil counts of $0.5\text{--}1.5 \times 10^9/\text{l}$ (mild-to-moderate neutropenia) are not associated with a significantly increased risk of infection.⁶ Agranulocytosis in this context is defined as neutrophil counts of $<0.5 \times 10^9/\text{l}$, where the case fatality rate is between 2% and 4%.⁷

Current data suggest that COVID-19 infection results in a lowered white cell count (WCC) of $<4.0 \times 10^9/\text{l}$ for between 9 and 45% of patients.^{8–12} Lymphocytopenia (lymphocytes $<1.5 \times 10^9/\text{l}$) is especially common, being reported in 33–83% of patients.^{8–13} More severe abnormalities correlate with severity of the disease; lower counts are seen

in those for whom infection is fatal. In contrast, studies in COVID-19 patients have found neutrophils to be in the normal range ($3.0\text{--}7.5 \times 10^9/\text{l}$).^{8,9,13} There are no published data describing neutrophil counts in COVID-19-positive patients taking clozapine.

We present a series of patients who contracted COVID-19 whilst taking clozapine. Neutrophil counts and WCCs are illustrated for the period prior to contracting COVID-19, during the infection, and after recovery.

Method

All patients were either inpatients at South London and the Maudsley NHS Foundation Trust at the time of testing positive for COVID-19 or admitted to the neighbouring acute trust and were under the care of the psychiatric liaison team. The ANC taken a minimum of 14 days prior to a positive nasopharyngeal swab for viral ribonucleic acid of SARS-CoV-2 was used as a ‘baseline’ ANC level. The day of the positive COVID-19 swab was designated as day 0. The

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Table 1. Demographic characteristics of total sample.

	<i>n</i> (N=13)
Mean age in years (range)	48 (19–75)
Male	4
Ethnicity	
Black British	3
Black and White	1
Nigerian	2
Caribbean	2
Indian/British Indian	1
White	4
BEN diagnosis	2
Frequency of clozapine FBC monitoring	
Weekly	1
Fortnightly	1
Monthly	11

BEN, benign ethnic neutropaenia; FBC, full blood count.

mean ANC and WCCs for days 0–7 and days 8–14 are reported. Data were analysed using IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, USA) and means compared using paired samples *t*-tests. Approval for this study was granted by the trust's drug and therapeutics committee.

Results

Data for 13 consecutive patients (9 female, 4 male) are presented (Table 1). The mean age was 48 years at the time of the positive swab, and nine patients were of non-White background. All except two patients had their regular clozapine full blood count taken monthly and had therefore been taking clozapine for more than a year. Two had a prior diagnosis of benign ethnic neutropaenia (BEN).

The mean ANC at baseline was 4.83×10^9 , reducing to 4.24×10^9 in the first week following a positive COVID-19 swab (Table 2). Mean ANC for the second week was 5.70×10^9 . No ANC was taken in the time period between days 8 and 14 for one patient; the next available ANC was used as representative of the post-infection

ANC count. Three patients died in the week after testing positive; their data are included in the baseline and week 1 mean ANC but missing for week 2. Two of the patients that died were women, two were of non-White heritage and one had a BEN diagnosis. All had been on clozapine for more than a year. The mean age at death was 65 years. Medical comorbidities are outlined in Table 2. The cause of death was given as COVID-19 pneumonia in two cases, and myocardial infarction in the third.

There were no statistically significant differences between mean ANC at baseline and days 0–7 after the positive COVID-19 result ($p=0.240$), between the mean ANC on days 0–7 and days 8–14 ($p=0.155$), or between baseline ANC and mean ANC on days 8–14 ($p=0.509$; Figure 1).

Discussion

This case series shows that no statistically significant change in ANC occurred in patients taking clozapine who tested positive for the novel coronavirus SARS-CoV-2. We observed no clear trend for reduction in neutrophil counts during infection. There are two major clinical implications. First, clozapine should generally be continued during coronavirus infection. Second, patients taking clozapine who experience neutropaenia whilst suffering from COVID-19 should be investigated and monitored as per normal practice, as it cannot be assumed to be secondary to the viral infection.

Viral infections, including influenza, commonly cause neutropaenia, either by suppressing bone marrow production or accelerating peripheral destruction.¹⁴ Data from the COVID-19 outbreak in China suggest that patients with COVID-19 infection frequently present with low WCC.^{8,11,13} This appears to be due to reduced lymphocytes. Lymphocytopenia in patients with COVID-19 is shown to be predictive of disease progression, correlating with high levels of interleukins 6 and 8 and a severe or critical clinical outcome.¹⁵ The increase in inflammatory cytokines causes a rise in neutrophils as part of the initial antiviral immune response.¹⁶

The data we present here show no significant change in neutrophil counts but faintly suggest an initial small fall in neutrophil counts followed by a rise, in line with expected immune responses to viral infection. Clozapine-induced neutropaenia is an

Table 2. Clinical details and mean ANC and WCC for each time period.

Patient	Length of time on clozapine	BEN	Medical comorbidities	Mean ANC ($\times 10^9$)		Mean WCC ($\times 10^9$)		Outcome	
				Baseline	Days 0–7	Baseline	Days 0–7		Days 8–14+
A	>1year	No	None	2.91	3.45	5.39	5.10	5.00	Survived
B	0–18weeks	No	Postural tachycardia syndrome	3.65	4.63	6.24	6.60	5.61	Survived
C	>1year	Yes	None	5.21	2.78	8.19	6.31	6.25	Survived
D	18–52weeks	No	Microcytic anaemia	3.47	4.75	8.4	8.86	8.82	Survived
E	>1year	No	None	2.56	2.54	4.8	3.80	5.19	Survived
F	>1year	No	Anaemia	2.49	1.48	6.5	4.95	5.71	Survived
G	>1year	No	Type 2 diabetes mellitus, hypertension, obesity	11.2	10.10	15.69	12.67	26.79	Survived
H	>1year	Yes	Type 2 diabetes mellitus, chronic obstructive pulmonary disease, chronic anaemia and neutropaenia, essential thrombocytopenia, hypercholesterolaemia, gastro-oesophageal reflux disease, gout, hypertension	2.37	1.60	4.79	2.62	N/A	Died
I	>1year	No	Type 2 diabetes mellitus	4.92	2.96	7.41	4.35	8.01	Survived
J	>1year	No	Type 2 diabetes mellitus, thalassaemia, cataracts,	5.09	4.02	8.27	5.68	9.24	Survived
K	>1year	No	Type 2 diabetes mellitus, end-stage renal failure, thromboembolic disease, ileostomy	6.86	9.68	8.98	11.80	N/A	Died
L	>1year	No	Type 2 diabetes mellitus, psoriatic arthropathy, overactive bladder	7.2	3.31	9.2	4.80	4.75	Survived
M	>1year	No	Type 2 diabetes mellitus, chronic obstructive pulmonary disease, hypertension, hypothyroidism, osteoporosis	4.9	3.78	8.1	4.99	N/A	Died
Mean ($\times 10^9$), (range)				4.83 (2.37–11.20)	4.24 (1.48–10.10)	7.84 (4.79–15.69)	6.35 (2.62–12.67)	8.54 (4.75–26.79)	

ANC, absolute neutrophil count; N/A, not available; WCC, white cell count.

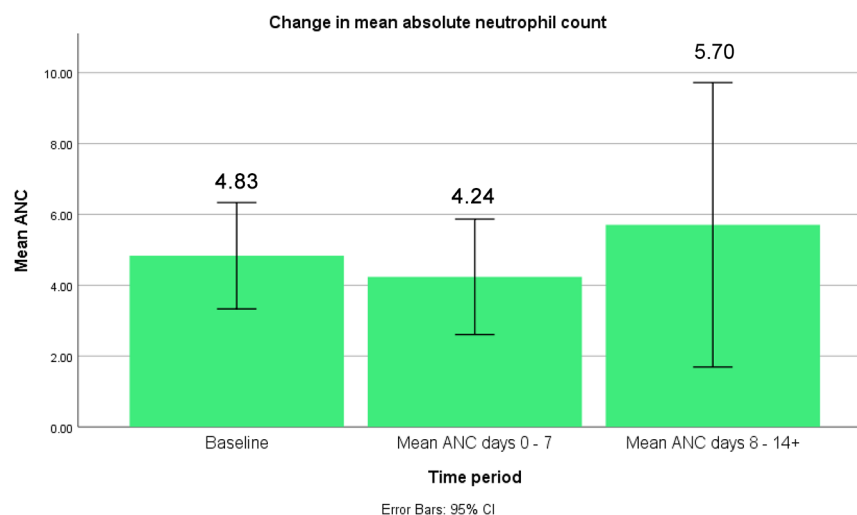


Figure 1. Change in mean ANC. No statistically significant differences between mean ANC at each time point. ANC, absolute neutrophil count; CI, confidence interval.

idiosyncratic reaction, possibly mediated by direct binding of metabolites to neutrophils¹⁷ and is rare beyond the first 3 months of treatment. It therefore seems unlikely that taking clozapine would predispose patients to adverse haematological effects in viral infections, since the immune response of neutrophils to inflammatory cytokines is not affected.

COVID-19 infection does not appear to cause a significant or prolonged neutropaenia in patients taking clozapine. Patients should therefore continue to receive clozapine and be assessed for the possibility of clozapine-induced neutropaenic sepsis if they present with fever, cough, myalgia, fatigue or shortness of breath,¹⁸ bearing in mind that this is an extremely rare event in patients who have been established on treatment for more than 3 months.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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