Case Report
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Clozapine in the Time of COVID-19

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Clozapine is the most effective antipsychotic for treatment resistant schizophrenia but adverse reactions to clozapine include neutropenia. The current COVID-19 pandemic may raise specific concerns for clinicians prescribing clozapine for patients who need it. We report on two actively psychotic patients with treatment resistant schizophrenia who required admission to our inner-London acute psychiatric unit during the COVID-19 pandemic and who were treated with clozapine. One was a young patient who developed COVID-19 symptoms and tested positive for the SARS-CoV-2 virus while receiving clozapine and the other was an aging man who tested negative for the SARS-CoV-2 virus but had contact with COVID-19 during initiation of clozapine treatment. Both responded to clozapine treatment and were safely discharged from hospital without any complication. These cases suggest that, in the absence of complications, exposure to COVID-19 per se and the onset of mild symptoms in those infected may not warrant withdrawal or postponement of clozapine treatment when this is indicated.

KEY WORDS: Clozapine; COVID-19; Coronavirus; Psychotic disorders; SARS-CoV-2; Schizophrenia.

INTRODUCTION

Whereas the coronavirus disease 2019 (COVID-19) has been shown to have a benign and self-limiting course in most people [1], in severe cases complications have included acute respiratory distress syndrome, sepsis, cardiac failure, respiratory failure and death [2]. Case mortality is currently estimated at between 1% and 7% [3], with both the elderly and those with medical comorbidities at greatest risk.

Patients with schizophrenia may be vulnerable to COVID-19 complications due to the high prevalence of comorbid metabolic disorders [4]. Social deprivation, high prevalence of smoking, obesity and side effects of psychotropic treatments may also potentially contribute to worse outcomes. Prescribing for patients with treatment resistant schizophrenia may pose pressing questions to clinicians. Clozapine, the drug of choice for schizophrenia patients who fail to respond to other antipsychotics, is associated with 3.8% risk of neutropenia [5], but the impact of clozapine treatment in the presence of COVID-19 is unknown.

We report on two actively psychotic patients with treatment resistant psychosis admitted to our inner-London acute psychiatric unit during the COVID-19 pandemic, and who were treated with clozapine. One was a young patient who tested positive for SARS-CoV-2 virus while receiving clozapine and the other was an aging man who had contact with patients with COVID-19 during initiation of clozapine treatment. Both responded to clozapine treatment and were safely discharged from hospital without any complication.

CASE

Continuing Clozapine Treatment

A 21 year-old man with an established diagnosis of treatment resistant schizoaffective disorder was admitted following a psychotic relapse. He presented as perplexed, with thought disorder and responding to auditory hallucinations. He had been started on clozapine 18 months prior to admission after failing to respond to different anti-

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psychotics. He had responded favourably to clozapine 850 mg orally single dose associated with lithium carbonate 1.2 g orally single dose at night and had relapsed as a result of erratic compliance with treatment.

He was restarted on his regular doses of clozapine and lithium. On day 7 of his admission, his serum clozapine level was 710 ng/ml on point-of-care testing [6] and his daily dose was reduced to 800 mg nocte. On day 10, he developed coryzal symptoms and a temperature of 39°C. Physical observation revealed a resting pulse rate of 129 beats/min, blood pressure of 167/140 mmHg, oxygen saturations of 95% on air and a normal respiratory rate. There were no cardiac symptoms suggestive of myocarditis and no muscle rigidity or hyporeflexia suggestive of neuroleptic malignant syndrome. Blood tests showed mildly deranged renal function (serum creatinine of 142 μmol/L, estimated glomerular filtration rate of 77 ml/min), raised inflammatory markers (C-reactive protein 15.5 mg/L, neutrophil count 6.94 × 10^9/L) and normal troponin-T and creatinine kinase levels. Red and white cell counts were both within normal range. The patient was placed in isolation and barrier nursed. A nasal and oral swab was positive for SARS-CoV-2 virus. Clozapine was withheld while investigation results were pending, during which time he remained severely thought disordered, with chaotic behaviour.

After he had been monitored for 72 hours, his clozapine was re-titrated over a period of 5 days to a total daily dose of 600 mg. His renal function deteriorated further on day 16 (serum creatinine 190 μmol/L, estimated glomerular filtration rate of 30 ml/min), which was thought to be a result of poor oral intake while in isolation. Lithium was withheld, oral intake monitored closely and the patient prompted to increase his fluid intake. On day 18, lithium was re-introduced following resolution of the patient's acute kidney injury. On day 20, his psychotic symptoms had markedly ameliorated. He appeared more coherent, engaged constructively with the clinical team and his family confirmed 'he was back to his usual self'. He was receiving clozapine 600 mg nocte and lithium 400 mg nocte. His trough whole blood clozapine level, measured using point-of-care testing [6], was 211 ng/ml (therapeutic range 250 to 350 ng/ml). He had fully recovered from COVID-19 and was safely discharged back to his family home under the care of community services.

Starting Clozapine Treatment

A 67 year-old man with a diagnosis of treatment resistant paranoid schizophrenia was admitted with long-standing grandiose delusions of vast financial wealth, over which he had minimal insight and as a result of which he had lost his job years ago, accrued major financial debts and had long become estranged from his family. His admission was prompted by his severely deteriorating clinical status following disengagement from community services. He had previously been treated with aripiprazole, risperidone and olanzapine, but responded only partially to each. He had no known medical co-morbidity and smoked 20 cigarettes a day.

After a 3-week retrial of risperidone proved unsuccessful, initiation of clozapine was considered despite his advancing age. As he had been in contact with other patients on the ward who had contracted COVID-19, there were concerns he might have been infected, but a throat and nose swab for SARS-CoV-2 virus was negative. With the patient's informed consent, his dose of clozapine was titrated up to 150 mg twice a day over a period of a week. He developed an isolated sinus tachycardia (rate 110–125 beats per minute) with no associated cardiac symptoms or changes in his blood pressure, oxygen saturations, respiratory rate and temperature. Routine blood tests, including renal function tests, inflammatory markers (white cell count, C-reactive protein) and serial troponin-T levels, were all within normal limits.

He remained on clozapine 300 mg single dose at night for further two weeks, during which period he experienced a remarkable improvement of his psychotic symptoms, with the virtual resolution of his delusions followed by his willing re-engagement with the clinical team. Clozapine plasma level following titration was 250 ng/ml. He was discharged back home under the care of community services.

DISCUSSION

Clozapine is the most effective antipsychotic for reducing positive symptoms, is widely used [7] and is the best, if not the only, therapeutic option for patients with treatment resistant schizophrenia [8]. Interruption of clozapine treatment can precipitate dramatic psychotic relapses in patients who have responded to it [8], while delays in starting clozapine could mean many wasted years

of otherwise treatable psychosis to those who need it [9]. In the absence of guidelines, clinicians prescribing clozapine during the COVID-19 pandemic will have to optimise the use of the resources available and weigh the risks and benefits for each individual patient.

In the first case, we decided to restart the patient's clozapine despite his symptoms of confirmed COVID-19, after a brief interval and under close medical monitoring, and in the knowledge that he had responded to it when he complied with his treatment. As he was young and had no medical comorbidity, the risks associated with discontinuing his clozapine treatment, namely the exacerbation of his psychotic symptoms, were thought to far outweigh the risks associated with receiving clozapine, as well as lithium, while experiencing COVID-19 symptoms. The second patient was an elderly man whose highly impairing psychotic symptoms had long been left untreated, and for whom the opportunity to be started on clozapine had to be considered in the light of risk factors associated with both clozapine itself (e.g., neutropenia) and the COVID-19 pandemic. Although he tested negative for the SARS-CoV-2 virus, he had been exposed to COVID-19 patients, and his age group and longstanding smoking habit could increase the risk of COVID-19 complications in case he developed symptoms following a viral infection [3]. Both patients responded to clozapine treatment and could be safely discharged from hospital without any complication a few weeks after being admitted.

Both patients clearly benefited from clozapine. These two cases suggest that, in the absence of complications, exposure to COVID-19 per se and the onset of mild symptoms for those infected may not warrant withdrawal or postponement of clozapine treatment when this is indicated. Moreover, COVID-19 health and safety guidelines which apply to acute inpatient units seem adequate for treatment-resistant patients who are actively psychotic and require admission to hospital and should include SARS-CoV-2 testing for all patients and robust isolation policies for those tested positive. Similarly, general guidelines for the clinical management of COVID-19 also seem appropriate for this patient group. Measurement of clozapine levels should be used to monitor therapeutic response. The newly introduced point of care testing of whole blood clozapine levels [6] is as reliable as measurement of clozapine plasma levels for this purpose, but can be obtained in 7 minutes rather than days, thus informing dose titration, expediting clinical decisions and facilitating patients' discharge from hospital. Longer term prescribing of clozapine in the community during the COVID-19 pandemic should address risk factors for each individual patient and be adjusted accordingly [10]. Absolute neutrophil count monitoring is important. It is unclear how coronaviruses may affect neutrophils in patients receiving clozapine, and changes in clozapine dosing may be required in the presence of COVID-19 symptoms.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Luiz Dratcu. Data acquisition: Xavier Boland. Writing—original draft: Xavier Boland. Writing—review and editing: Luiz Dratcu.

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