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

Clozapine toxicity and coronavirus disease 2019: A case report

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Dear editor,

The ongoing coronavirus disease 2019 (COVID-19) pandemic is posing multiple unprecedented challenges to psychiatrists all over the world. So far, there is no data on COVID-19 infections and clozapine, the most effective antipsychotic agent for refractory schizophrenia. Nevertheless, the peculiarities of this drug have entailed the prompt release of specific articles and guidelines for adjustment of its prescription and monitoring (De Leon et al., 2020; Siskind et al., 2020; South London and Maudsley National Health Service Foundation Trust, 2020). Main concerns are (a) safety issues and complicated access to the required periodic absolute neutrophil count monitoring (2); (b) association of clozapine with higher rates of pneumonia, which seem to be primarily driven by increased risk of aspiration -due to sedation and sialorrhea- and also impaired immunological mechanisms (De Leon et al., 2020; Kuo et al., 2013); (c) symptom overlap between clozapine-induced neutropenic sepsis and COVID-19 manifestations (South London and Maudsley National Health Service Foundation Trust, 2020); and (d) risk of a rise in clozapine blood levels related to a serious infection such as SARS-CoV-2 (Clark et al., 2018). To our knowledge, we report the first case of clozapine toxicity due to COVID-19.

Our patient was an institutionalized 68-year-old man with a diagnosis of schizophrenia with predominant negative symptoms. His somatic comorbidities included peripheral arthropathy, type II diabetes, occasional fecal and urinary incontinence, chronic constipation and monostotic Paget's disease. He did not smoke or have any other substance use disorder. His home medication included clozapine 375 mg/day, clotiapine 60 mg/day, alprazolam 1.5 mg/day and trazodone 100 mg/day, as well as macrogol oral powder twice daily and pentoxifylline 800 mg/day. He had been mentally stable for many years. Clozapine had been added more than ten years ago, with no serious adverse effects and no major changes in dosage; serum levels had systematically been within therapeutic range.

The patient presented to our emergency department with dyspnea, tachypnea, dry cough, asthenia and malaise. No fever was reported. Symptoms had begun two weeks before and had progressively worsened. He was diagnosed with bilateral pneumonia and required hospitalization. COVID-19 etiology was verified by molecular detection. Upon admission, serum clozapine and norclozapine levels were 1094 ng/mL (normal range 250–600 ng/mL) and 284 ng/mL, respectively, with a ratio of 3.8:1 (normal range 0.5–3:1 [Couchman et al., 2010]; previous ratios of patient 1.3–1.8:1). On physical examination, the patient was somnolent and mildly hypotensive; he did not develop neutropenia, hyperthermia, seizures, cardiac arrhythmias or any other serious complications. Prior to blood sampling, medications added to his home treatment were prophylactic enoxaparin (40 mg/day) and a first dose of ceftriaxone (1 g/day continued for seven days), which have no known interactions with clozapine; afterwards, hydroxychloroquine (400 mg/day for ten days) and azithromycin (500 mg on day one followed by 250 mg/day for the next four days) were also administered. Clozapine dosage was immediately reduced to 200 mg/day, which led to prompt normalization of serum levels and clozapine:norclozapine ratio, as well as resolution of signs of toxicity. As the patient recovered from his pneumonia, clozapine was progressively readjusted with instructions for reaching prior dosage levels as an outpatient. He was discharged to his residential facility sixteen days after admission. Using the Naranjo Adverse Drug Reaction Probability Scale (Naranjo et al., 1981), we determined that the onset of clozapine toxicity may have been related to the patient's COVID-19 infection.

In subjects with inflammatory diseases, a three- to five-fold increase in clozapine plasma levels has been described in many series and case reports (Clark et al., 2018). An underlying metabolic mechanism seems to play the main role: inflammation leads to the production of interleukin-6 (IL-6), which downregulates the expression of cytochrome P450 1A2 and, therefore, inhibits clozapine metabolization -as well as others such as imipramine- (Doude van Troostwijk et al., 2003; Morgan, 2009); consequently, clozapine accumulates and levels rise. As in other inflammatory diseases, SARS-CoV-2 infections have also been reported to increase IL-6 (Coomes and Haghbayan, 2020), so this same mechanism may be responsible for the clozapine toxicity we report. Our clozapine:norclozapine ratio also supports this claim, as high ratios (>3) suggest inhibition or saturation of metabolism (Kuo et al., 2013). In fact, recommendations on the use of clozapine during the COVID-19 pandemic include close monitoring of patients who become symptomatic and reduction of dosage if signs of toxicity appear, in the awareness of the theoretical risk of a rise in levels in the event of an acute systemic

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infection (De Leon et al., 2020; Siskind et al., 2020). With this case report, we provide real-world evidence of this possibility; therefore, we reinforce the aforementioned recommendations and highlight the need for clinicians to acknowledge the risk of clozapine toxicity due to COVID-19.

Contributors

No other contributors apart from the authors.

Declaration of competing interest

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The other authors have no conflicts of interest to disclose.

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References

Clark, S.R., Warren, N.S., Kim, G., Janokowiak, D., Schubert, K.O., Kisley, S., Forrester, T., Baune, B.T., Siskind, D.J., 2018. Elevated clozapine levels associated with infection: a systematic review. Schizophr. Res. 192, 50–56. https://doi.org/10.1016/j.schres.2017.03.045.

Coomes, E.A., Haghbayan, H., 2020. Interleukin-6 in COVID-19: A Systematic Review and Meta-Analysis. MEDRXIV. https://doi.org/10.1101/2020.03.30.20048058 [preprint].

Couchman, L., Morgan, P.E., Spencer, E.P., Flanagan, R.J., 2010. Plasma clozapine, norclozapine, and the clozapine:norclozapine ratio in relation to prescribed dose and other factors: data from a therapeutic drug monitoring service, 1993–2007. Ther. Drug Monit. 32 (4), 438–447. https://doi.org/10.1097/FTD.0b013e3181dad1fb.

De Leon, J., Ruan, C.J., Schoretsanitis, G., De las Cuevas, C., 2020. A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. Psychother. Psychosom. 14, 1–15. https://doi.org/10.1159/000507638.

Doude van Troostwijk, L.J., Koopmans, R.P., Vermeulen, H.D., Guchelaar, H.J., 2003. CYP1A2 activity is an important determinant of clozapine dosage in schizophrenic patients. Eur. J. Pharm. Sci. 20 (4–5), 451–457. https://doi.org/10.1016/j.ejps.2003.09.010.

Kuo, C.J., Yang, S.Y., Liao, Y.T., Chen, W.J., Leem, W.C., Shau, W.Y., Chang, Y.T., Tsai, S. Y., Chen, C.C., 2013. Second-generation antipsychotic medications and risk of pneumonia in schizophrenia. Schizophr. Bull. 39 (3), 648–657. https://doi.org/10.1093/schbul/sbr202.

Morgan, E.T., 2009. Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics. Clin. Pharmacol. Ther. 85 (4), 434–438. https://doi.org/10.1038/clpt.2008.302.

Naranjo, C.A., Busto, U., Sellers, E.M., Sandor, P., Ruiz, I., Roberts, E.A., et al., 1981. A method for estimating the probability of adverse drug reactions. Clin. Pharmacol. Ther. 30, 239–245. https://doi.org/10.1038/clpt.1981.154.

Siskind, D., Honer, W.G., Clark, S., Correll, C.U., Hasan, A., Howes, O., Kane, J.M., Kelly, D.L., Laitman, R., Lee, J., MacCabe, J.H., Myles, N., Nielsen, J., Schulte, P.F., Taylor, D., Verdoux, H., Wheeler, A., Freudenreich, O., 2020. Consensus statement on the use of clozapine during the COVID-19 pandemic. J. Psychiatry Neurosci. 45 (4), 200061 https://doi.org/10.1503/jpn.200061.

South London, Maudsley National Health Service Foundation Trust, 2020. Clozapine and Blood Dyscrasias in Patients With Coronavirus (COVID-19). Available from:, 1st edition. National Health Service Foundation Trust, London https://www.rcpsych.ac.uk/about-us/responding-to-covid-19/responding-to-covid-19-guidance-for-clinicians/community-and-inpatient-services/providing-medication.

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