Elevated clozapine levels and toxic effects after SARS-CoV-2 vaccination

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Case studies indicate that coronavirus disease 2019 (COVID-19) can be associated with toxic clozapine levels, requiring monitoring to maintain therapeutic levels and prevent relapses of psychotic or new rash. His temperature was 37.0°C, pulse was 129 beats/minute, and blood pressure was 151/86 mm Hg. A chest radiograph showed subsegmental atelectasis or scarring; the lungs were otherwise clear, and an area of consolidation observed previously was resolved. Intra-venous antibiotics were started empirically. Blood and urine cultures were negative, as was reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2, influenza and respiratory syncytial virus. A computed tomography scan of his head obtained to investigate delirium showed changes suggesting undiagnosed normal pressure hydrocephalus.

At admission, the patient’s neuropsychological test results were normal pressure hydrocephalus. He was admitted to hospital out of concern for infection. There was no cough, diarrhea, nausea, vomiting or new rash. His temperature was 37.0°C, pulse was 129 beats/minute, and blood pressure was 151/86 mm Hg. A chest radiograph showed subsegmental atelectasis or scarring; the lungs were otherwise clear, and an area of consolidation observed previously was resolved. Intra-venous antibiotics were started empirically. Blood and urine cultures were negative, as was reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2, influenza and respiratory syncytial virus. A computed tomography scan of his head obtained to investigate delirium showed changes suggesting undiagnosed normal pressure hydrocephalus.

The patient had received yearly influenza vaccinations without complication. During a hospital admission for pneumonia treated with intravenous antibiotics, while taking 500 mg/d clozapine, his clozapine level was elevated (Table 1) and he was over-sedated. Thereafter he was stabilized on 300 mg/d with a plan to monitor his clozapine level monthly.

As part of routine care, the patient received the Pfizer-BioNTech vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19. Adverse events began on the fourth day following vaccination. The patient became delirious, fell repeatedly and was increasingly incontinent. He was admitted to hospital out of concern for infection. There was no cough, diarrhea, nausea, vomiting or new rash. His temperature was 37.0°C, pulse was 129 beats/minute, and blood pressure was 151/86 mm Hg. A chest radiograph showed subsegmental atelectasis or scarring; the lungs were otherwise clear, and an area of consolidation observed previously was resolved. Intra-venous antibiotics were started empirically. Blood and urine cultures were negative, as was reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2, influenza and respiratory syncytial virus. A computed tomography scan of his head obtained to investigate delirium showed changes suggesting undiagnosed normal pressure hydrocephalus.

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lymphoid tissues — all features observed in healthy volunteers given the mRNA vaccine, and consistent with findings in our patient. Detection of a “danger signal” by immune cells leads to the production of proinflammatory cytokines, such as interleukin-6, that bind to receptors on hepatocytes, leading to release of acute phase proteins, such as CRP. The CRP level is a highly sensitive inflammatory biomarker that can reach levels 1000-fold or more above baseline, with a response time of 6–12 hours and a rapid decrease 18–20 hours following termination of an inflammatory challenge.

Inflammation can inhibit drug metabolizing enzymes through 3 proposed mechanisms: induction of transcriptional regulators, induction of nitric oxide–dependent proteosome degradation of enzymes, and epigenetic modification resulting in decreased gene expression. Clozapine and theophylline levels are sensitive to inflammation-related inhibition of CYP1A2 activity. These complex patterns of stimulation and response are incompletely understood and may explain why different stimuli affect drug levels in a specific manner. Notably, yearly vaccination for influenza had no symptomatic consequences in our patient, consistent with the reported absence of effect of influenza vaccination on clozapine levels reported by others. Influenza vaccine has been associated with mild changes in immune cell profile and a wide range of CRP responses that may be related to dose, different adjuvant components of vaccines, or individual differences in immune system exposures or genetics.

During the COVID-19 pandemic, the approach to managing clozapine in a patient with fever or flu-like symptoms includes obtaining clozapine levels in patients with symptoms possibly indicating toxicity, reducing the dose by as much as half, continuing the lower dose until symptoms subside, and then increasing stepwise to the previous dose. This single case we report cannot establish a causal relationship between vaccination and elevated clozapine level; more clinical reports and research are required. Multiple predisposing factors may have contributed risk for symptomatic expression of the high clozapine level in our patient, including age, structural brain abnormalities, multiple medical comorbidities and concurrent medications. The complex immunomodulatory effects of clozapine may contribute to increased rates of pneumonia; the earlier pneumonia-related high clozapine level in our patient may represent individual sensitivity to specific types of inflammatory stimuli.

In summary, patients can continue to be treated with clozapine during SARS-CoV-2 infection; similarly, there is no reason to avoid vaccination. Careful evaluation for symptoms consistent with clozapine toxicity following SARS-CoV-2 vaccination and obtaining clozapine and CRP levels when indicated may help maintain patients safely on clozapine — particularly patients with risk factors including previous high clozapine levels related to infection or inflammation — and prevent relapse of psychotic illness.

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**Competing interests:** D. Thompson is an unpaid reviewer for the Canadian Council on Continuing Education in Pharmacy program on clozapine, which received funding from HLS Therapeutics. She also received payment for presenting at a drug-induced movement disorder workshop and the University of British Columbia Continuing Pharmacy Education Conference and received an honorarium from the Canadian Pharmaceutical Association for lecturing chapters on psychiatric and substance use topics for the *Compendium of Pharmaceutical Choices*. She is an unpaid member of the British Columbia Schizophrenia Society Medical Advisory Board. R.F. White has received honoraria from HLS Therapeutics. W.G. Honer has received consulting fees or sat on paid advisory boards for Translational Life Sciences, AbbVie and Guidepoint. C. Delorme reports no competing interests.

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