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Letter to the Editor

Serotonin syndrome in two COVID-19 patients treated with lopinavir/ritonavir



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Dear Editor,

Serotonin syndrome (SS) is a potentially life-threatening drug-induced disorder mediated by serotonergic over-activity at synapses of the central and peripheral nervous system [1]. The fixed combination of lopinavir/ritonavir (LPV/r) has been widely used during the present Coronavirus Disease 2019 (COVID-19) pandemic [2]. Ritonavir has, however, been shown to trigger SS in HIV-infected individuals [3]. We here provide the first report of two COVID-19 patients who developed SS.

1. Patient 1

A 66-year-old male with a previous history of hypertension, bipolar disorder, and cervical spinal stenosis was admitted with bilateral pneumonia due to reverse transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19. LPV/r 400 mg/100 mg plus 200 mg of hydroxychloroquine, both twice daily, were started, while maintaining his previous lithium (800 mg/day) and duloxetine (120 mg/day) treatment. By day-3 he developed delirium, and 1 mg of haloperidol twice daily was added. For the next 4 days, his level of consciousness progressively declined, in association with high blood pressure, tachycardia, diaphoresis, and urinary retention. A neurological examination revealed obtundation, with the patient only capable of emitting unintelligible sounds and obeying single orders; multifocal facial, appendicular, and axial myoclonus; and generalized hyperreflexia with ankle clonus, without significant rigidity. His blood CK level increased to 767 U/L and his creatinine level increased to 1.47 mg/dL from previously normal values, while his lithium level remained normal. An electroencephalogram revealed diffuse encephalopathy, while brain magnetic resonance imaging did not result in any significant findings. Due to SS suspicion, duloxetine, lithium, haloperidol, and LPV/r were discontinued. Cyproheptadine at 8 mg every 6 h was started. This resulted in improvement of the myoclonus, but it had to be withdrawn due to excessive somnolence. Over the next 10 days, the myoclonus disappeared and his neurological status improved steadily.

2. Patient 2

A 78-year-old male with a history of hypertension, diabetic chronic kidney disease, and prior colorectal cancer was admitted with mild respiratory symptoms secondary to COVID-19 confirmed by RT-PCR of a nasopharyngeal swab. Oxygen and treatment with lopinavir/ritonavir (LPV/r) 400 mg/100 mg plus 200 mg of hydroxychloroquine, both twice daily, was initiated. Additionally, two doses of interferon beta-1b were administered on days 3 and 4, and a single administration of tocilizumab on day-9 due to a sustained fever, progressive dyspnea that required a higher oxygen flow with a reservoir, and radiologic deterioration consistent with bilateral pneumonia. By day-10 the patient developed acute delirium that required 1 mg of risperidone twice daily for the next 48 h and a single administration of 3 mg of morphine for dyspnea control. Subsequently, the patient's level of consciousness worsened, and he developed tachycardia, diaphoresis, and hyperthermia that was unresponsive to antipyretics. A neurological examination revealed confusion, ocular clonus, multifocal limb myoclonus of moderate amplitude, hyperreflexia, and mild cogwheel rigidity of all four limbs (see Supplementary Video 1). His blood creatine kinase (CK) level increased from previously normal levels to 802 U/L and his creatinine level increased from 1.06 mg/dL to 1.93 mg/dL. An electroencephalogram revealed diffuse encephalopathy and his brain computed tomography scan was unremarkable. As SS was suspected, LPV/r and risperidone were immediately discontinued, instead adding fluid therapy, active cooling, and 0.25 mg of clonazepam every 6 h. The symptoms rapidly improved and resolved within the next several days.

3. Discussion

SS constitutes a dose-dependent spectrum of adverse effects associated with increased serotonergic activity, characterized by an altered mental state, autonomic overactivity highlighting tachycardia, diaphoresis, and hyperthermia, as well as movement disorders such as hyperreflexia with clonus, ocular clonus, myoclonus, tremors, or rigidity [4]. Both patients fulfilled this classical clinical triad.

SS is typically caused by the combination of selective serotonin (SSRIs) and serotonin-norepinephrine (SNRIs) reuptake inhibitors,

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monoamine oxidase inhibitors, tricyclic antidepressants, opiates, or lithium among others [1]. While malignant neuroleptic syndrome has traditionally been linked with antipsychotic drugs, second-generation antipsychotics (SGA) such as risperidone are also able to induce SS [5], mediated via its 5-HT_{2A} receptor antagonism, which can shunt elevated levels of serotonin to other receptors such as 5-HT_{1A} and thus increasing serotonin signaling [6]. Risperidone and morphine may also elevate 5-HT neurotransmission by acting on GABA interneurons in the dorsal raphe nucleus, which is the main central source of serotonin [7,8].

As the LPV/r combination has antiviral activity against SARS-CoV-1 and MERS-CoV [2], it has also been used to treat COVID-19. Ritonavir can trigger SS in patients with concomitant treatment with SSRIs and SNRIs, mainly due to diminished elimination [3]. As risperidone is a CYP2D6 and CYP3A4 substrate, both of which are inhibited by ritonavir, an increase in its serum concentrations can be expected. In our two reported cases, the respective administration of LPV/r with an SNRI (duloxetine) and lithium, and LPV/r with an SGA (risperidone) and morphine, resulted in a combination that presumably triggered typical SS. This is also supported by the rapid improvement of the symptoms after their withdrawal.

Note that a very low dose of clonazepam (0.25 mg/6 h) was used to manage severe myoclonus in the second patient, once LPV/r was discontinued. However, co-administration of LPV/r and clonazepam may increase the concentration of the latter due to its metabolism by CYP3A4. A reduction in clonazepam dose may be necessary and therapeutic concentration monitoring is recommended [9].

To our knowledge, this is the first report of SS in COVID-19 patients. As delirium is common in patients with COVID-19, and ritonavir has many interactions with antipsychotic drugs, we recommend, if necessary, considering olanzapine given its tendency to diminish its plasma levels, or alternatively lowering the dosage of other antipsychotics that would tend to accumulate. Most antidepressants also require a dosage adjustment when used with LPV/r [9].

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Declaration of Competing Interest

None.

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