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Consultation psychiatry in COVID-19 patients: Lopinavir/ritonavir interactions with main psychiatric drugs

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Within only about 7 months from its appearance, COVID-19 has rapidly spread across the globe, infecting (at the time of writing) more than 62 million worldwide and causing the death of more than 1 455 030 persons.[1] Several extant antivirals have been investigated as potential treatment options for COVID-19, including a combination of protease inhibitors lopinavir/ritonavir.[2] Front-line COVID-19 physicians should be well aware that the use of these drugs requires particular attention due to their possible adverse effects on the central nervous system, especially in the treatment of psychiatric patients and the vulnerable elderly population, characterized by many comorbidities and co-treatments.

In light of the above, the aim of this Letter is to briefly describe the possible interactions between lopinavir/ritonavir and psychotropic drugs.

Protease inhibitors are all metabolized in the liver by the cytochrome P450 (CYP) enzyme system, especially the CYP3A4 isoenzyme.[3] The CYP system is also the major hepatic enzyme complex involved in the metabolism of many other drugs, including most of the psychotropic drugs used in clinical practice. Its various isoenzymes can be either induced or inhibited by a number of agents and the protease inhibitors, particularly ritonavir, are among the most potent inhibitors of CYP3A4.[4] Ritonavir also has high inhibition potency against CYP-2C9, -2C19, and -2D6.[5] Moreover, it is also an inducer and inhibitor of p-glycoprotein.[6] This could lead to clinically relevant pharmacological interactions that physicians, when called on to deal with COVID-19 patients, must consider. Much of the data on drug interactions with protease inhibitors appear in product labeling information and in a few case-report studies, but many more pharmacological interactions and resulting clinical indications can be inferred from the pharmacokinetics and pharmacodynamics of psychiatric medications (see Table S1 and the references). There are different mechanisms by which lopinavir/ritonavir interact with psychiatric treatments (antidepressants, antipsychotics, and mood stabilizers):

1 *Inhibition of the cytochrome P450 isoforms implicated in the metabolism of psychoactive drugs*. This inhibition can reduce the clearance of many antidepressants, antipsychotics, and anxiolytics, increasing plasma concentrations of the main molecules and related major active metabolites that, in turn, will be able to exert therapeutic or collateral effects depending on the level and type of inhibition.In this mechanism, all protease inhibitors are involved but, for the reasons mentioned above, ritonavir is obviously the main actor. It is responsible for the main psychiatric contraindications indicated in the product labeling information (i.e., lurasidone, pimozide, quetiapine, midazolam, and triazolam) through its strong inhibition of CYP-3A4 but many other clinically relevant interactions with antidepressants and antipsychotics have been described in the literature[7] and many others can be deduced.Almost all monoaminergic modulators, such as selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and tricyclic antidepressants, can be affected by these interactions (see Table S1).
2 *Induction of the cytochrome P450 isoforms implicated in the metabolism of psychoactive drugs*. This induction can increase the clearance of different drugs, decreasing their plasma concentrations and, probably, the resulting clinical efficacy. Ritonavir has been shown to induce CYP-2B6 (e.g., bupropion), CYP-1A2 (e.g., olanzapine), and UDP-glucuronyltransferases (e.g., lamotrigine and valproate; see Table S1).
3 *Induction of the cytochrome P450 isoforms implicated in the metabolism of antivirals and reciprocal effects*. Protease inhibitors are also substrates of cytochrome activities and their levels can be modulated by inhibitors or inductors. Lopinavir levels and other antivirals can be decreased by different inducers.In the psychiatric context, the principal agent is *Hypericum perforatum* (St. John's wort), a herbal medicine used for its possible antidepressant activity and a potent inducer of CYP-3A4. Coadministration with St. John's wort may significantly reduce the plasma concentrations of HIV protease inhibitors and result in a potential loss of virologic response.[8] Coadministration with carbamazepine was reported to be particularly complex and unpredictable, as its induction on CYP-3A4 is potentially able to decrease protease inhibitor concentrations with the resulting potential antiretroviral resistance and treatment failure, and its levels may, at the same time, be boosted by ritonavir leading to carbamazepine-related toxicity[9] (see Table S1).
4 *Greater risk of QT prolongation*. Protease inhibitors could predispose individuals to QT prolongation and torsade de pointes[10] by dose-dependent block of human ether-a-go-go-related gene (*HERG*) potassium channels. Theoretically, coadministration with other agents that can prolong the QT interval – and the psychiatric pharmacopeia is full of QT prolongers – may result in additive effects and increased risk of ventricular arrhythmias, including torsade de pointes and sudden death.

Disclosure statement

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Supporting Information.

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