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Short Commentary

The Risk of Potential Drug-Drug Interactions in Patients Treated for SARS-CoV-2

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A year has passed since the detection of the first cases of pneumonia caused by the SARS-CoV-2 virus in the city of Wuhan, China. Since then, it has become a global pandemic with more than 100 million people infected and more than 2 million deaths [1]. At the beginning of the pandemic, there was no effective treatment or vaccine available to combat the respiratory infection caused by the virus, called COVID 19. For this reason, the initial treatment strategy was drugs with limited experience and evidence used in previous endemics caused by viruses of the coronavirus family. In this direction, the drug regulatory agencies of each country, in our case, the Spanish Agency for Medicines and Health Products (AEMPS), issued recommendations for the diagnosis and treatment of COVID 19. The basis of the recommended treatment consisted of the combination of drugs with antiviral activity such as lopinavir/ritonavir (LPV/r), hydroxychloroquine (HCQ) and remdesivir and drugs with anti-inflammatory or immunomodulatory activity such as tozilizumab, interferon Beta-1b and anakinra, among others [2]. One of the main drawbacks related to these medications are their potential drug-drug interactions (pDDI), which can trigger adverse effects or decrease the effectiveness of treatments. On the other hand, the population most susceptible to suffering from pDDI are elderly patients with comorbidity and polypharmacy [3]. In turn, the risk factors associated with severe disease due to COVID 19 are age>65 years and a previous pathological history such as cardiovascular disease [4]. Therefore, the activity performed by the clinical pharmacist in the surveillance and detection of pDDI has been of great importance in the prevention of drug-related problems.

One of the drugs most used initially against SARS-CoV-2 was LPV/r, a combination of antiretrovirals widely used in the treatment of HIV. Lopinavir has antiviral activity, while ritonavir acts as an enhancer, inhibiting metabolism and increasing plasma concentrations of lopinavir. It has a high profile of interactions due to the ability to modify the hepatic metabolism of other drugs, through the inhibition of CYP3A4 or induction of CYP2C9 and 2C19 and glucuronidation reactions, in addition to inhibiting transporter proteins such as P-glycoprotein [5]. HCQ was another drug used initially and associated with LPV/r, with in vitro antiviral activity against SARS-CoV-2 and with a high incidence of pDDI, mainly at the cardiac level, such as prolongation of the QT interval and increased risk of ventricular arrhythmia [6]

Throughout 2020, several studies have been carried out in two of the countries hardest hit by the first wave of the pandemic, Spain and Italy, with the aim of analyzing the pDDI associated with the experimental drugs used for the treatment of COVID 19 [7-10]. Our group was the first to evaluate the frequency of pDDI and identify the associated risk factors in a COVID 19 patient receiving LPV/r treatment. In our study, we included 364 patients with a pDDI rate of 62.3%, with 20.92% classified as risk X (medication contraindicated with LPV/r) and showing budesonide (inhaled route) and simvastatin as the drugs with the highest number of severe pDDI vs. LPV/r. Age>65 years, stay in the critical care unit, previous respiratory and psychiatric pathology, dyslipidemia, and the number of drugs prescribed behaved as independent variables of presenting a pDDI associated with LPV/r [7]. In another subsequent study with 125 COVID 19 patients receiving LPV/r treatment, the authors observed a 78% prevalence of pDDI and a mortality associated only with the Charlson comorbidity index [8]. Another work by the Italian group by Cattaneo et al, evaluated the incidence of pDDI in a cohort that included 399 COVID 19 patients with at least 2 active treatments, showing an incidence of PDDI of 68%, with 55% classified as severe pDDI related mainly to HCQ and LPV/r. The proportion of patients with severe pDDi increased from 22% in the initial phase of admission to 80% during admission, with cardiovascular risk being the main secondary problem of pDDI [9]. Finally, we found a very interesting work by Martinez-López-de-Castro et al, who, in addition to determining the prevalence of pDDI of all the drugs used for the treatment of COVID 19 (HCQ, LPV/r, tocilizumab and interferon Beta 1b) evaluated the clinical repercussions of the same. The frequency of pDDI was 62.3%, produced mainly by LPV/r and HCQ. 5.7 % of the patients treated with HCQ and evaluated by electrocardiogram (ECG) presented significant clinical alteration of the QT interval. 7.3% had a non-cardiological adverse reaction possibly related to pDDI. Hyperglycemia, gastrointestinal disturbances, skin reactions, and increased sedative effect were the main clinical implications [10].

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For the identification and recommendation of the pDDI, different check databases were used, available on platforms such as https://covid19-druginteractions.org/. This website created and promoted during the pandemic by the University of Liverpool, a leading entity in the screening and recommendation of pDDI in HIV patients, is a useful tool for the management of pDDI in COVID 19 patients. But the use of databases to pDDI identification is not without limitations. In the screening of interactions, clinical pharmacists found slight discrepancies between reference databases, for example, in the severity or risk level of the interaction, which makes it difficult to establish recommendations. On the other hand, some databases detect interactions only between drug pairs, while the interaction screening must be carried out for the complete treatment of the patient, because there are drug combinations that may have an unaccounted summation pharmacodynamic effect, such as prolongation of the QT interval.

In conclusion, drugs with a high incidence of pDDI used in the treatment of COVID 19 should be evaluated and reviewed by the clinical pharmacist in order to establish recommendations to reduce drug-related problems associated with pDDI, to the extent of as possible.

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