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Perspective

Benefits of Lopinavir against Ritonavir in Virtual Patients with COVID-19

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DESCRIPTION

The Serious Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) is the cause of the coronavirus illness 2019 (COVID-19), which has been spreading all over the globe. Although COVID-19 therapies have not yet been established, there is indication that they are in the development process. Because ritonavir's Pharmacokinetic (PK) booster effect was employed to treat COVID-19, lopinavir/ritonavir (LPV/r) was previously used in this capacity. However, LPV/r was left out of the Japanese COVID-19 therapy guidelines since the results of an open-label randomized controlled trial showed that it is an ineffective treatment for the disease. However, the LPV/r dosage in the aforementioned trial was 400 mg/100 mg twice daily, which does not quantitatively reach the dosage necessary for the PK booster effect. Instead, this trial was carried out at doses that were 400 mg/100 mg, which were those that were licensed for the treatment of Human Immunodeficiency Virus (HIV) infection. As a result, it is too early to draw any conclusions about LPV/effectiveness for COVID-19, and more pharmacokinetic validation is required to evaluate its therapeutic potential.

The generic antiviral medication nirmatrelvir and the antiviral medication ritonavir, collectively known as paxlovid, have been shown to be a successful treatment for COVID-19 in a clinical trial run by Pfizer. Although the US Food and Drug Administration (FDA) have not yet approved paxlovid for the treatment of COVID-19, Health Canada has approved. Nirmatrelvir, the main medication in paxlovid, is intended to inhibit the SARS-CoV protease, an enzyme required for the virus to replicate. Nirmatrelvir's metabolism is slowed by low-dose ritonavir, which is a characteristic of a PK booster, and this prolongs the drug's activity at higher concentrations. However, because the PK booster effect for patients with HIV infection or COVID-19 was different from that for healthy participants, these individuals did not reach the reference range at the same dose. The concentrations were well beyond the effective range in healthy volunteers given the recommended dose, but 74.4% of the subjects in the steady-state above the safety limit, raising questions about potential adverse effects. The recommended dose was insufficient to treat the patient with COVID-19. The findings demonstarted that the approach of raising the ritonavir dose to 600 mg produced an ideal percentage of coverage within the effective range and plateaued with further augmentation.

Ritonavir's PK booster action reduces CYP3A4 activity and raises LPV concentration. It's interesting to note that patients with COVID-19 or HIV infection have been shown to have 50% and 22% less CYP3A4 activity, respectively, than healthy volunteers. These results suggest that individuals with COVID-19 or HIV infection would require a lower dose of ritonavir than healthy volunteers. The study indicates that COVID-19 patients would require a greater ritonavir dose than healthy volunteers. Therefore, taking into account CYP3A4 activity and IC50 values, the PK booster effect was calculated. Based on the PK booster effect, the reduction in lopinavir clearance for healthy volunteers and patients with COVID-19 was 88% and 25%, respectively. This study gives a conclusion that COVID-19 patients require a greater ritonavir dose than the healthy volunteers.

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