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Pharmacokinetics of lopinavir/ritonavir oral solution to treat COVID-19 in mechanically ventilated ICU patients

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Background: The combination lopinavir/ritonavir is recommended to treat HIV-infected patients at the dose regimen of 400/100 mg q12h, oral route. The usual lopinavir trough plasma concentrations are 3000–8000 ng/mL. A trend towards a 28 day mortality reduction was observed in COVID-19-infected patients treated with lopinavir/ritonavir.

Objectives: To assess the plasma concentrations of lopinavir and ritonavir in patients with severe COVID-19 infection and receiving lopinavir/ritonavir.

Patients and methods: Mechanically ventilated patients with COVID-19 infection included in the French COVID-19 cohort and treated with lopinavir/ritonavir were included. Lopinavir/ritonavir combination was administered using the usual adult HIV dose regimen (400/100 mg q12h, oral solution through a nasogastric tube). A half-dose reduction to 400/100 mg q24h was proposed if lopinavir C_{trough} was >8000 ng/mL, the upper limit considered as toxic and reported in HIV-infected patients. Lopinavir and ritonavir pharmacokinetic parameters were determined after an intensive pharmacokinetic analysis. Biological markers of inflammation and liver/kidney function were monitored.

Results: Plasma concentrations of lopinavir and ritonavir were first assessed in eight patients treated with lopinavir/ritonavir. Median (IQR) lopinavir C_{trough} reached 27 908 ng/mL (15 928–32 627). After the dose reduction to 400/100 mg q24h, lopinavir/ritonavir pharmacokinetic parameters were assessed in nine patients. Lopinavir C_{trough} decreased to 22 974 ng/mL (21 394–32 735).

Conclusions: In mechanically ventilated patients with severe COVID-19 infections, the oral administration of lopinavir/ritonavir elicited plasma exposure of lopinavir more than 6-fold the upper usual expected range. However, it remains difficult to safely recommend its dose reduction without compromising the benefit of the antiviral strategy, and careful pharmacokinetic and toxicity monitoring are needed.

Introduction

Approximately 25% of hospitalized patients infected with SARS-CoV-2 will require ICU admission.[1] Several antiviral strategies are currently being tested.[2] In a recent randomized controlled trial, the lopinavir/ritonavir combination showed no significant clinical benefit compared with placebo in adults hospitalized with confirmed COVID-19 infection.[3] However, it showed a trend in reducing 28 day mortality in the most severe cases, especially when treatment was started early. The lopinavir/ritonavir combination is approved for treatment of HIV, but pharmacokinetic parameter alteration in mechanically ventilated patients in the ICU might have contributed to the relative lack of efficacy. We thus aimed to describe further the potential pharmacokinetic alterations observed in severely ill patients with COVID-19 infections.

Methods

The selected dose regimen was based on the experience in HIV treatments with lopinavir/ritonavir (Kaletra™ oral solution, AbbVie™, USA) at the dose of 400/100 mg q12h (full dose). The day the treatment was initiated was defined as Day 0 (D0q12h). Since patients were intubated and placed under mechanical ventilation early after ICU admission, the enteral route through a nasogastric tube was preferred. After 3 days of treatment at full dose, the trough plasma concentrations (C_{trough}) of lopinavir/ritonavir were measured using UPLC-MS/MS (Waters, USA).[4] In HIV-infected patients receiving the 400/100 mg q12h dose regimen, the upper limit of lopinavir C_{trough} is 8000 ng/mL.[5] Real-time monitoring was performed for interpretation of lopinavir C_{trough}. If patients presented a lopinavir C_{trough} >8000 ng/mL, the dosage regimen was reduced to a 'half dose' (400/100 mg q24h), to anticipate and avoid toxicity. The day the treatment at half dose was initiated was defined as Day 0 (D0q24h). Two days after the dose reduction, an intensive plasma pharmacokinetic analysis was performed. Blood samples were drawn pre-dose and 1, 3, 4, 5, 7, 9, 12 and 24 h post-dose. The lower limit of quantification for both lopinavir and ritonavir was 15 ng/mL and the upper limit of linearity was 50000 and 5000 ng/mL, respectively. Of note, none of the measured lopinavir concentrations was >50000 ng/mL. The pharmacokinetic parameters measured were AUC_{0-24} determined using the composite trapezoid method, and the approximate half-life of elimination in hours. To evaluate potential determinants of the fluctuations in lopinavir concentrations, inflammation parameters were closely monitored, and liver and renal tests were assessed to monitor potential toxicity. Linear mixed effects regression was performed when applicable.

Ethics

Patients' data were prospectively collected in a database, supported by the National French Scientific Institute for Medical Research and the REACTing Network. The study is part of the overall French COVID-19 cohort assessing patients with COVID-19 and registered in clinicaltrials.gov (NCT04262921). It was approved by the French ethics committee, and consent was obtained from each patient involved.

Results

At the start, eight patients received the full dose of lopinavir/ritonavir; the median (IQR) age was 52 years (49–54). The median (IQR) SOFA score at admission was 2 (2–3). No liver or renal failure was observed at admission. All patients were placed under invasive mechanical ventilation within the first 48 h and had a median (IQR) SOFA score of 4 (3–4) at D0q12h. The median (IQR) C-reactive protein (CRP) level was 186 mg/L (99–281) (Tables S1 and S2, available as Supplementary data at *JAC* Online).

After 3 days of full-dose administration, median (IQR) C_{trough} values of lopinavir and ritonavir were, respectively, 27908 (15928–32627) and 634 ng/mL (255–1269). Overall, all patients presented lopinavir C_{trough} >8000 ng/mL. Thus, these patients were eligible for the half-dose regimen. However, two patients were extubated after the first half-dose and no intensive pharmacokinetic analysis was performed. Also, one patient was withdrawn from lopinavir/ritonavir treatment because of an adverse event (cholestasis).

In light of these elevated lopinavir C_{trough} values, we decided to start the half dose in four other patients. Therefore, nine patients started the lopinavir/ritonavir half dose (D0q24h) (Figure 1). They were all mechanically ventilated, with a median (IQR) SOFA score of 9 (8–11) at D0q24h. Four patients (44%) underwent renal replacement therapy. The median (IQR) CRP level was 237 mg/L (155–286) (Tables S1 and S3).

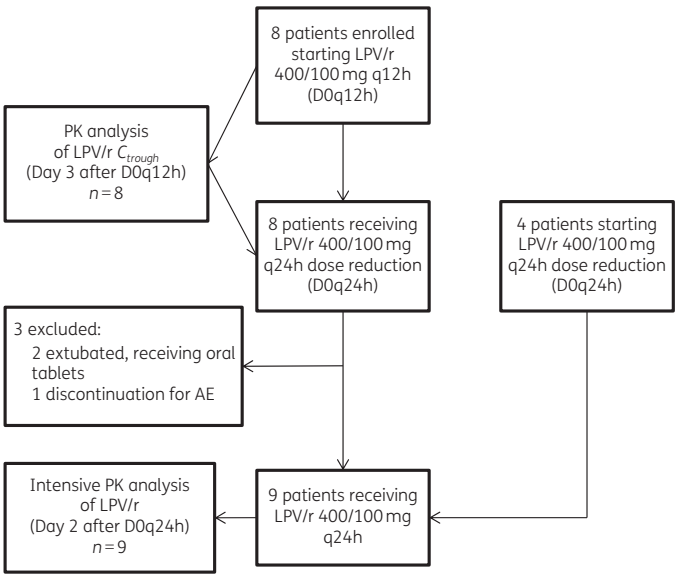

Figure 1. Flow chart of COVID-19 ICU patients receiving lopinavir/ritonavir 400/100 mg q12h as oral solution through a nasogastric tube, then receiving 400/100 mg q24h. Pharmacokinetic analysis timings are shown. AE, adverse event; LPV/r, lopinavir/ritonavir; PK, pharmacokinetic.

After 2 days of the half-dose regimen, the median (IQR) pharmacokinetic parameters for lopinavir were: AUC_{0-24} 668788 ng·h/mL (546219–829593); C_{trough} 22974 ng/mL (21394–32735); and $t_{1/2}$ 178.2 h (63.0–244.4). For ritonavir, the median (IQR) pharmacokinetic parameters were: AUC_{0-24} 13069 ng·h/mL (6324–18596); C_{trough} 186 ng/mL (15–474); and $t_{1/2}$ 19.6 h (8.8–47.8) (Figure 2).

We performed a linear mixed effects regression between CRP and lopinavir C_{trough}, including both q12h and q24h dosing regimen values, with a positive correlation between the two parameters ($P=0.0387$) (Figure S1).

During the full-dose regimen period ($n=8$), we noted an increase in γ-glutamyl transpeptidase (γGT), alkaline phosphatase (ALP), total bilirubin and creatinine plasma levels, with a positive variation of 74%, 55%, 113% and 110%, respectively (Table S2). During the half-dose regimen period ($n=9$), we observed an increase in γGT, ALP and creatinine plasma levels with a positive variation of 60%, 22% and 12%, respectively (Table S3).

Of note, the two patients who were withdrawn from the intensive pharmacokinetic analysis after receiving the half-dose regimen were weaned from invasive ventilation, with a median (IQR) duration of ventilation of 12 days (10–13). For these patients, lopinavir/ritonavir C_{trough} decreased, within 48 h of the dose reduction, to 4462/118 and 379/15 ng/mL, respectively. CRP plasma levels were 41 and 28 mg/L, respectively. The lopinavir/ritonavir 400/100 mg (tablets) q12h dosing regimen was then resumed for 5 days.

Discussion

In our ICU, we investigated the plasma concentrations of lopinavir/ritonavir administered to COVID-19-infected patients at the usual dose regimen of 400/100 mg q12h given via a nasogastric tube

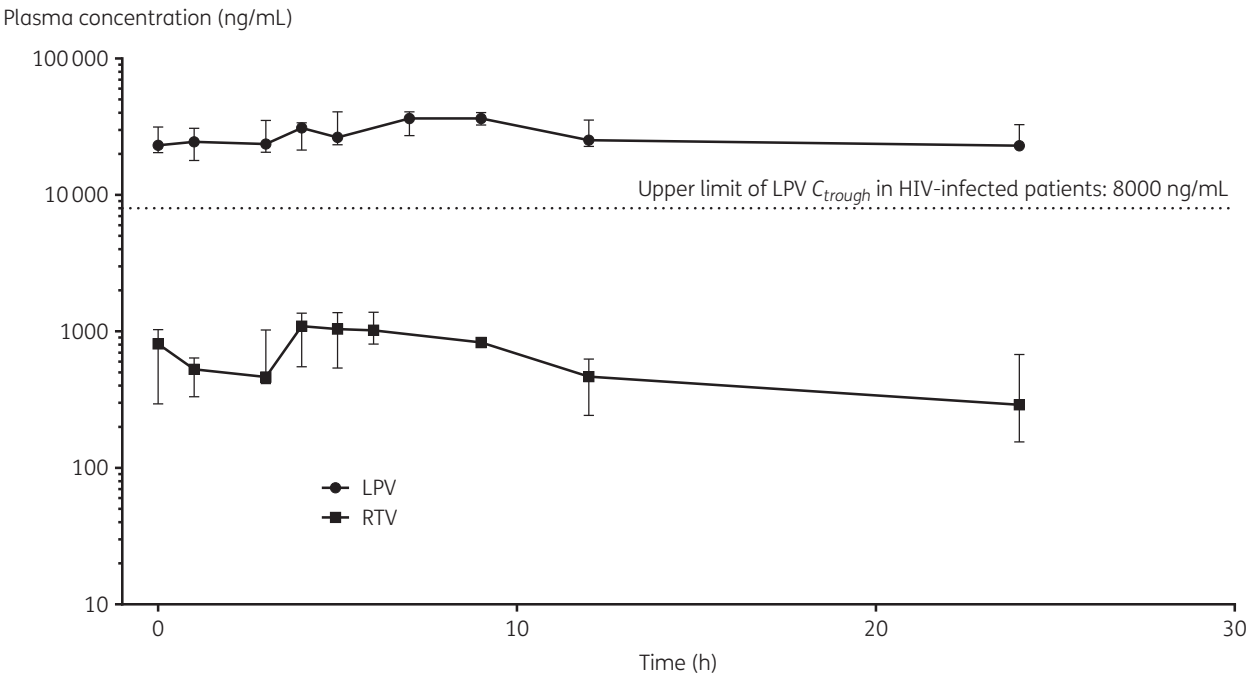

Figure 2. Lopinavir (LPV) and ritonavir (RTV) total (median, IQR) plasma concentrations in patients treated with LPV/RTV oral solution at 400/100 mg q24h dosing regimen ($n = 9$). The upper limit of LPV C_{trough} in HIV-infected patients was set as 8000 ng/mL as reported by González de Requena *et al.*[5]

during enteral nutrition. Since all patients presented lopinavir C_{trough} >8000 ng/mL, we chose to empirically reduce the dosing regimen for our patients to avoid additional hepatotoxicity. We also observed that a lopinavir C_{trough} >20000 ng/mL was reached on halving the dose (400/100 mg q24h) in approximately 75% of our patients [who presented with significant inflammation (plasma CRP >200 mg/L)]. The median (IQR) AUC_{0-24} of lopinavir in these patients [668788 ng·h/mL (546219–829593)] was increased compared with HIV-infected patients (AUC_{0-12} 113200 ± 60500 ng·h/mL),[6] and led to much higher plasma exposure of lopinavir than expected, even if we extrapolate the 12–24 h interval by doubling the AUC_{0-12} of HIV patients. This might partially explain the increase in liver test values. Surprisingly, the ritonavir C_{trough} values at 400/100 mg q24h were lower than those in the q12h dosing regimen. These results were similar to those measured in HIV patients receiving the 400/100 mg q12h dosing regimen.

The considerable increase in drug exposure that we observed could be explained by different mechanisms. First, this might be explained by a high and prolonged absorption rate and a slow elimination rate. Indeed, lopinavir and ritonavir are lipophilic compounds (logP octanol/water 5.9 and 6.0, respectively). The use of high-lipid enteral nutrition might have enhanced their absorption. The food effect (872 kCal, lipid 55%) increased the AUC of lopinavir by 130% when administering oral solution.[6] Gastrointestinal paresis prompted by deep sedation and the effect of neuromuscular blocking agents required for the invasive mechanical ventilation might allow prolonged uptake of the latter compounds.

Another potential explanation of the high C_{trough} obtained with the usual dose regimen is related to the cytokine storm associated with severe COVID-19 infections. Indeed, viral infection with SARS-CoV-2 elicits a high production of cytokines (IL-1β, IL-1, TNF-α, IL-6, IFN, TGF-β), which are known to down-regulate CYP3A4,[7] thus leading to a slower elimination rate of lopinavir/ritonavir.

Of note, the interruption of sedative drugs, gastric motility improvement and the use of oral tablets and standard feeding as well as the decrease in the inflammatory process might have resulted in lower concentrations of lopinavir, which allowed resumption of the usual q12h dose regimen for two patients.

No data on hepatotoxicity are available after a short course of 5 days of treatment.[8] Among our patients, we found an increase in γGT, ALP and total bilirubin, but the highest values stayed under twice the upper bound (Table S2). We also observed an increase in plasma creatinine level, with four patients who required renal replacement therapy. In the literature, nephrotoxicity of lopinavir/ritonavir is reported when combined with NRTIs in treatment of HIV infection, caused by induced mitochondrial toxicity.[9,10] Despite the high plasma concentration of lopinavir/ritonavir found in our four patients, we do not have enough data to allocate the acute kidney failure to the drugs only.

The main limitations of our pragmatic report would be the absence of a comparative study design allowing the evaluation of lopinavir/ritonavir and its dosing regimen safety versus a standard-of-care arm.

Conclusions

In patients with severe COVID-19 infections who were mechanically ventilated and received enteral nutrition, the oral administration of lopinavir/ritonavir resulted in major alterations of lopinavir

pharmacokinetic parameters. Our results suggest that careful pharmacokinetic and toxicity monitoring is needed if lopinavir/ritonavir is used to treat severe COVID-19 infections. However, without pharmacodynamic data on lopinavir/ritonavir efficacy against COVID-19 and its efficacy threshold, it remains difficult to safely recommend its dose reduction without compromising the benefit of the antiviral strategy. Our results highlight the urgency of a comprehensive pharmacokinetic/pharmacodynamic analysis for the upcoming clinical trials in similar critically ill patients with COVID-19 infection.

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Supplementary data

Tables S1–S3 and Figure S1 are available as Supplementary data at *JAC* Online.

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