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Crushing lopinavir/ritonavir tablets does not result in lower exposure to lopinavir/ritonavir in adult patients with COVID-19

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ABSTRACT

Objective Lopinavir/ritonavir (LPV/RTV) exposure is decreased in children after crushing the tablets. Whether exposure is also decreased in adult patients is not known. This study evaluated the exposure of LPV/RTV in adult patients after administration of crushed LPV/RTV tablets.

Methods Blood samples were drawn from patients with COVID-19 who were receiving crushed LPV/RTV 400/100 mg tablets twice daily.

Results Plasma concentrations for 11 patients with COVID-19 (eight men, mean age 62.6 years) were included. The measured plasma concentrations of LPV were substantially higher than reported for patients with HIV.

Conclusions There is adequate exposure from crushed LPV/RTV tablets, but because of limited experience, therapeutic drug monitoring is still advised.

INTRODUCTION

Lopinavir (LPV) is an HIV protease inhibitor that has shown inhibitory activity against Middle East respiratory syndrome coronavirus (MERS-CoV) in vitro and in an animal model.¹ Furthermore, it LPV has shown inhibitory activity in vitro against severe acute respiratory syndrome coronavirus (SARS-CoV).^{2,3} At the beginning of the coronavirus infection disease 2019 (COVID-19) outbreak caused by SARS-CoV-2, which belongs to the same genera of coronaviruses, LPV was mentioned as one of the potential (off-label) therapeutic options for COVID-19 and was declared as the preferred treatment in the first version of the Dutch treatment guideline.^{4,5}

During the start of the COVID-19 outbreak, the availability of Kaletra oral solution was limited in The Netherlands. Therefore, the oral solution was reserved for (future) paediatric patients with COVID-19. Adult patients who could not swallow and/or had a nasogastric tube were treated with crushed LPV/ritonavir (RTV) tablets (generic tablets, Accord Healthcare BV). This practice is not in accordance with the product information, which states that LPV/RTV tablets should not be broken, chewed or crushed.⁶

LPV and RTV are poorly soluble drugs (Biopharmaceutics class 2 or 4).⁷ Melt-extrusion technology has been used to obtain a solid dispersion of LPV and RTV in a polymer to optimise transfer of these drugs into the aqueous environment of the gastrointestinal tract. This polymer is further processed into

tablets.⁸ Crushing of these tablets disturbs the solid dispersion formulation and can result in a decreased bioavailability of LPV and RTV.^{9,10}

A study in children has shown that administration of crushed LPV/RTV tablets, compared with intact tablets, reduced the exposure to LPV and RTV with a decrease in area under the curve (AUC) by 45% and 47%, respectively.¹⁰ Based on these data, administration of crushed tablets is not recommended, or in case this is unavoidable, a higher dose and therapeutic drug monitoring would be required.¹⁰

METHODS

The variable oral bioavailability of LPV and RTV and the data about reduced exposure after crushing of tablets were reasons for us to measure LPV and RTV plasma concentrations to determine whether adequate exposure was reached in the first group of patients with COVID-19 treated in the intensive care unit of the Elisabeth-TweeSteden hospital. This Dutch hospital was one of the first where a large group of patients with confirmed or suspected SARS-CoV-2 infection were hospitalised and treated.

In this letter we evaluate the retrospectively available data from the exposure of LPV and RTV administered as crushed tablets through a nasogastric tube in adult patients with COVID-19 in our hospital. The measured plasma concentrations of LPV were compared with historical mean population LPV concentrations for patients with HIV.⁶

RESULTS

We obtained data for 11 patients with COVID-19 (eight men, mean age 62.6 years, range 50–77 years). All patients had an estimated glomerular filtration rate (eGFR, expressed as Chronic Kidney Disease Epidemiology Collaboration) greater than 60 mL/min/1.7 m², except for patient number 8 who had an eGFR of 49 mL/min/1.7 m². A dose modification for LPV/RTV was not necessary with this eGFR.

With the exception of patients 7, 8 and 11, all the other patients had mild elevated ALT (range 56–113 U/L) and AST (range 49–156 U/L). An increase in γ -glutamyl transferase (GGT) was seen in patients 2, 4, 9 and 10 (range 93–217 U/L). None of patients had an elevated bilirubin. No dose reduction was needed in any of our patients based on the hepatic function. We assume that with these



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Table 1 An overview of measured plasma samples with patient characteristics, therapy duration with LPV/RTV, time between last administrated LPV/RTV dose and measured plasma concentration of LPV/RTV

Patient number	Sample	Gender	Age (years)	Weight (kg)	Duration LPV/RTV treatment (days)	Time between last dose of LPV/RTV and measurement (hours)	Plasma concentration LPV (mg/L)	Plasma concentration RTV (mg/L)	Constipation	Gastric retention
1	1	M	57	85	5.5	10	>30	0.65	Yes	Yes
2	1*	M	67	90	5.5	10	10.8	0.19	Yes	Yes
2	2*	M	67	90	7.5	12.5	7.1	0.28	Yes	Yes
3	1	M	77	73	6.5	10	19.05	0.53	Yes	Yes
4	1	F	65	95	3.5	10.5	9.9	0.20	Yes	Yes
5	1	M	52	99	4.0	9.5	20.1	0.64	Yes	No
6	1*	M	70	102	4.0	9	29.8	0.46	Yes	No
6	2*	M	70	102	6.5	9.5	23.7	0.37	No	No
7	1	M	65	107	3.0	11.5	28.8	0.53	Yes	No
8	1	F	70	129	2.5	11	9.8	0.37	Yes	Yes
9	1	M	52	93	2.0	9.5	>30	1.05	Yes	Yes
10	1*	M	50	128	2.5	9.5	28.4	0.52	Yes	No
10	2*	M	50	128	4.5	10.5	>30	0.44	Yes	No
11	1	F	64	104	2.0	9.5	19.7	1.92	Yes	Yes

*Samples from same patient, applies for patient number 2, 6 and 10.
F, female; LPV, lopinavir; M, male; RTV, ritonavir.

mild to moderate elevated liver enzymes there will be only a very limited effect on the exposure of LPV/RTV.¹¹

All patients received 400/100 mg LPV/RTV twice daily. All patients also used chloroquine (loading dose of 600 mg, followed by 300 mg twice daily for a total of 5 days). Chloroquine tablets were also crushed and administrated through a nasogastric tube. Blood samples were drawn 9–12.5 hours after the previously administrated dose of LPV/RTV. The duration of LPV/RTV treatment was variable at the moment of plasma concentration measurement (2–7.5 days). In three patients there were two subsequent plasma concentrations measured. The measured LPV plasma concentrations were substantially higher than the average population LPV concentrations of 5 mg/L for adults with HIV (table 1).⁶ None of the patients used any medication known to influence the pharmacokinetics of LPV/RTV, with the exception of chloroquine, which was administrated to all patients.

DISCUSSION

Our results are not in accordance with the results from the study in children, where a lower exposure of LPV and RTV was observed after crushing the tablets.¹⁰ There might be several explanations for this finding.

First, all patients had delayed gastric emptying and/or constipation at the time of blood sampling or on the preceding day. Constipation and gastric retention result in a longer gastrointestinal transit time, increasing the time for LPV to dissolve and be absorbed, thereby the bioavailability of LPV/RTV could be improved. Additionally, compared with children, the impact on the amount of LPV to dissolve when crushing these tablets might be smaller in adults because a higher dose/solubility ratio is expected in children.^{9 12}

Second, all patients used chloroquine in addition to LPV/RTV as a part of their SARS-CoV-2 treatment. Chloroquine is a mild P-glycoprotein inhibitor, and LPV and RTV are both transported by P-glycoprotein.^{13 14} The increased exposure of chloroquine by LPV/RTV could result in a moderate inhibition of P-glycoprotein by chloroquine and a higher exposure of LPV.¹⁵

Another possible contributing factor for the high LPV plasma concentration could be an alteration of cytokine profiles due to inflammation, which was the case for our patients considering their SARS-CoV-2 infection.^{16 17} Interleukin (IL)-1, IL-2 and IL-6 are known to inhibit cytochrome P450 (CYP) 3A4 activity.^{18–21} LPV is metabolised by CYP3A4 and therefore inhibition of this enzyme by cytokines could also result in higher plasma concentrations.⁶

Our retrospective analysis has limitations. In particular, the time when blood samples were drawn was not optimal. RTV induces metabolic enzymes, which results in the induction of its own metabolism (auto-induction) and that of LPV. Therefore, concentrations of LPV can be higher shortly after the start of administration.⁶ It is possible that LPV levels could decrease after several days when full auto-induction has not developed yet. Furthermore, because all the patients had delayed gastric emptying and/or constipation we cannot determine whether this is a major factor for the observed exposure to LPV/RTV.

Our results suggest that there is adequate exposure to LPV/RTV after administration of crushed tablets in the standard dose. Based on these results, we cannot recommend increasing the LPV/RTV dose in adult patients with COVID-19 when tablets need to be crushed. Because of the limited experience with crushed LPV/RTV tablets, therapeutic drug monitoring in future cases is still advised.

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