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RESEARCH LETTER

Lopinavir-Ritonavir Treatment for COVID-19 Infection in Intensive Care Unit

Risk of Bradycardia

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At the start of the coronavirus disease 2019 (COVID-19) outbreak in Europe, specific antiviral treatments were based on previous experience with SARS-Cov-1 (severe acute respiratory syndrome–coronavirus 1) and MERS-Cov (Middle East respiratory syndrome–related coronavirus) and on early experience with SARS-Cov-2 in China.[1] One of the promising treatment was the combination of lopinavir (LPV) and ritonavir (RTV; Kaletra; Abbott Laboratories, Chicago, IL), previously used for the treatment of SARS-Cov-1 and MERS-CoV infections. LPV is a protease inhibitor of HIV-1 that is usually combined with RTV, another protease inhibitor that strongly inhibits hepatic CYP (cytochrome P450; CYP3A4) activity, to increase LPV plasma concentration and efficacy, with limited side effects.[1,2] Separately, LPV is rapidly metabolized and has very low bioavailability.[2] At the start of the outbreak, decision was made in our institution to treat COVID-19 critically ill patients with LPV/RTV. For HIV-1 patients, a risk of bradycardia was reported possibly due to nodal toxicity of LPV/RTV.[3] To date, there are no data on bradycardia related to LPV/RTV treatment for COVID-19 critical ill patients. The aim of this prospective preliminary study was to record the risk of bradycardia for COVID-19 patients treated with LPV/RTV.

During the first month of the outbreak, patients admitted in our intensive care unit with a positive real-time polymerase chain reaction for COVID-19 (on a nasopharyngeal swab) received LPV (200 mg)/RVT (50 mg) BID for 10 days. Bradycardia was defined as heart rate <60 beats per minute for a period of >24 hours. All patients were monitored 24 hours a day for all hemodynamic parameters including heart rate with 5-lead ECG. Monitors were linked to a computerized system allowing to extract hemodynamic data. LPV/RTV plasma concentration was monitored using an analytical method combining high-performance liquid chromatography and tandem mass spectrometry at 72 hours and every 72 hours. This was an ancillary study of a larger study evaluating the outcomes of critically ill COVID-19 patients (NCT04354558). Patients were divided into 2 groups according to the presence of bradycardia and then compared (Fisher exact or Mann-Whitney *U* test). A Spearman rank correlation between heart rate and plasma level of LPV/RTV was performed. The limit of statistical significance was $P<0.05$. All statistical analyses were performed with IBM SPSS software (SPSS, version 24; IBM, New York, NY). All data and supporting materials have been provided with the published article. Written informed consent was waived by the Amiens University Hospital IRB (Comite de Protection des Personnes Nord-Ouest II CHU, Place V. Pauchet, 80054 AMIENS Cedex 1).

We prospectively included 41 COVID-19 patients who received LPV/RTV treatment. Nine (22%) patients experienced bradycardia (Table). No patient had preexisting nodal pathology on the ECG on admission. Among the 9 cases of bradycardia, 8 (88%) were sinus bradycardia and 1 (12%) third-degree atrioventricular block. Causality may be considered as bradycardia occurred at least 48 hours after LPV/RTV initiation, bradycardia resolved after discontinuation or dose reduction of LPV/RTV, and no alternative cause was found. Patients who presented with bradycardia were older (73 [62–80] versus 62 [54–68] years; $P=0.009$), had a higher RTV plasma concentration at 72 hours (1249 [820–1374] versus 652 [406–1176] ng·mL^{-1}; $P=0.036$), and had a lower lymphocyte count

Key Words: bradycardia ■ COVID-19 ■ critical illness ■ humans ■ lopinavir ■ ritonavir

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Table. Comparison of Patients With and Without Bradycardia

	No Bradycardia (n=32)	Bradycardia (n=9)	*P* Value
Age, y	62 (54–68)	73 (62–80)	0.009*
BMI, $kg{\cdot}m^{-2}$	30 (27–34)	27 (25–34)	0.273
Male sex, n (%)	21 (65)	7 (77)	0.39
SOFA score at ICU admission	6 (2–10)	8 (4–12)	0.31
Chronic medication use, n (%)			
ACE inhibitors	7 (21)	3 (33)	0.66
ARBs	5 (15)	3 (33)	0.34
β-Blocker	9 (28)	2 (22)	0.54
Diuretics	10 (31)	1 (11)	0.22
Calcium blocker	7 (21)	2 (22)	0.65
Days from onset symptoms to LPV/RTV treatment	8 (7–12)	11 (7–16)	0.23
Days from beginning of LPV/RTV to bradycardia	…	6 (2–8)	…
ECG at ICU admission			
Heart rate, bpm	88 (80–102)	88 (77–92)	0.69
P wave, ms	80 (60–100)	80 (60–100)	0.95
PR, ms	160 (152–180)	160 (160–180)	0.59
QRS, ms	90 (80–95)	95 (90–100)	0.21
QTc, ms	437 (420–460)	410 (380–440)	0.19
Biological data			
PaO_2/FiO_2 ratio	134 (80–157)	117 (102–180)	0.69
C-reactive protein, $mg{\cdot}L^{-1}$	185 (63–298)	158 (123–338)	0.96
Procalcitonin, $ug{\cdot}L^{-1}$	0.21 (0.12–1.4)	0.23 (0.14–1.2)	0.93
Lymphocyte count$\times 10^6$ L^{-1}	710 (600–800)	500 (265–1050)	0.006*
AST	49 (37–82)	41 (36–70)	0.87
ALT	34 (27–63)	37 (21–57)	0.89
aPTT	70 (60–81)	70 (69–79)	0.72
HS C troponin, ng·mL	141 (17–646)	16 (8–55)	0.37
BNP, pg·mL	60 (35–160)	33 (22–251)	0.58
Bradycardia characteristics on ECG			
Duration, h	…	48 (40–68)	…
Heart rate, bpm	…	46 (40–49)	…
Sinus bradycardia, n (%)	…	8	…
Third-degree AVB, n (%)	…	1	…
Serum potassium, $mmol{\cdot}L^{-1}$	…	4.3±0.7	…
Adjunctive therapy for bradycardia, n (%)			
Isoprenaline	…	1	…
Electrosystolic probe	…	1	…
Pacemaker	…	0	…
LPV/RTV dose reduction	…	4	…
LPV/RTV discontinuation	…	1	…
Drugs, n (%)			
Pantoprazole	17 (53)	3 (33)	0.45
Propofol	21 (65)	5 (55)	0.70
Midazolam	6 (18)	3 (33)	0.38
Sufentanyl	23 (71)	9 (100)	0.16
Vasopressors	23 (72)	8 (88)	0.41
Plasma level of RTV, ng/mL			
Day 3	652 (406–1176)	1249 (820–1374)	0.036*

(*Continued*)

Table. Continued

	No Bradycardia (n=32)	Bradycardia (n=9)	*P* Value
Day 7	539 (425–913)	617 (344–1417)	0.73
Plasmatic level of LPV, ng/mL			
Day 3	14 900 (10 120–21 480)	19 850 (14 960–21 945)	0.49
Day 7	13 640 (690–15 760)	16 350 (4211–24 240)	0.14
LPV/RTV duration, d	6 (4–9)	7 (6–9)	0.38
RTV cumulation dose, mg	650 (350–925)	900 (660–1150)	0.09
LPV cumulation dose, mg	2600 (1400–3700)	3600 (2650–4600)	0.10
Outcome			
Acute kidney injury	7 (22)	4 (44)	0.381
RRT	4 (58)	4 (100)	0.142
Mechanic ventilation	23 (71)	9 (100)	0.16
Death	6 (18)	2 (22)	1

Data are expressed as mean±SD, median (interquartile range) or numbers (percentage). ACE indicates angiotensin-converting enzyme; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; AVB, atrioventricular block; BMI, body mass index; BNP, B type natriuretic peptide; bpm, beats per minute; FiO_2, fraction of inspired oxygen; HS, high sensitive; ICU, intensive care unit; LPV, lopinavir; RRT, renal replacement therapy; RTV, ritonavir; and SOFA, sepsis-related organ failure assessment.

*Statistically significant ($P<0.05$).

(500 [265–105] versus 710 [600–800] $10^6 \cdot L^{-1}$; $P=0.006$). In our study, no correlation was found between RTV plasma concentration ($r^2=0.05$, $P=0.24$), LPV plasma concentration ($r^2=0.01$, $P=0.98$), and mean heart rate at day 3. No patient had bradycardia in the first 48 hours after LPV/RTV administration. For patients with LPV/RTV plasma level overdose, the dose of LPV/RTV was divided by 2 until the next dosage. For the patient with a third atrioventricular block, LPV/RTV was stopped. None of the patients had any known cytochrome CYP3A4-inhibiting drugs.

Our results suggest that RTV plasma overdose in elderly critical ill patients may increase the risk of bradycardia.

In HIV-1 patients, cases of bradycardia-tachycardia syndrome and bradyarrythmia were reported, but the underlining pathophysiological mechanism remains unclear.[3,4] Moreover, the use of LPV/RTV with drugs having an effect on the cardiovascular system could lead to bradycardia.[5] In the LPV/RTV trial for suppression of SARS-COV-2 in China, Cao et al[1] did not report any case of bradycardia. Compared with our study, their patients were less severe (only 15% on mechanical ventilation, no extracorporeal membrane oxygenation therapy) and younger (58 [50–68] years). Moreover, the majority of their patients did not have continuous heart rate monitoring during hospitalization, and no data on LPV/RTV plasmatic levels were reported.

LPVs have complex pharmacokinetic characteristics, especially, concentration/dose nonlinearity that explains why concentration increase is not proportional to dose increase. RTV increases oral drug adsorption via inhibition of P-glycoprotein—a membrane transport protein of digestive tract, whose expression and functionality can be modulated by factors such as inflammatory state, genetic polymorphism, or age with significant consequences on drug exposition and interaction.[6]

One hypothesis is that the inflammatory damage associated with COVID-19 increases intestinal absorption of RTV/LPV in elderly patients and increases the risk of bradycardia. The change in RTV/LPV doses administered and the decrease of inflammation during hospitalization could explain the regression of bradycardia. Nevertheless, bradycardia could be a sign of severe cardiological or neurological impairment since it is associated with lymphopenia that seems to reflect the severity of COVID-19 infection.

Intensivists should be aware of this potential side effect to closely monitor LPV/RTV plasma levels notably in elderly patients.

ARTICLE INFORMATION

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