



## Sex Differences in Lopinavir Concentrations and Occurrence of Marked QTc Prolongation Episodes in Patients with COVID-19

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Accepted: 13 November 2020 / Published online: 27 November 2020  
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Dear Editor,

We read with interest the article of Zekarias et al. [1] on sex-related differences to adverse drug reactions (ADRs) in patients with COVID-19. The authors extracted case safety reports from VigiBase, and found that there were more reports on hydroxychloroquine (HCQ, 864 reports) and lopinavir/ritonavir (LPV/r, 309) in male patients than in female patients (HCQ 612 and LPV/r 160, respectively). The most commonly reported ADRs were similar for female and male subjects except for the prolonged QT interval, which was documented in 31% of male reports and 19% of female reports ( $p = 0.01$ ). This sex-related difference on QT interval prolongation is in contrast to what has been reported in the literature, as this event typically occurs more frequently in female patients than it does in male patients [1]. We support the authors' findings with our prospectively collected data and provide a scientific rationale for the sex difference related to both the clinical course of COVID-19 and the occurrence of ADRs.

We previously investigated the effect of a systemic inflammatory response to SARS-CoV-2 on LPV and HCQ plasma concentrations in patients admitted to the University Hospital in Basel between 25 February and 30 April, 2020 [2]. Patients received LPV/r for 5–7 days combined with HCQ for 2 days [2]. For the present study, we specifically investigated sex differences in plasma concentrations of the cytochrome P450 (CYP) 3A4 substrate LPV and the occurrence of corrected QT (QTc) prolongation episodes in the

same COVID-19 cohort. Lopinavir plasma trough concentrations were routinely measured 2 or 3 days after initiating treatment and an electrocardiogram was performed at admission and repeated 3 days after. Additional electrocardiogram measurements were performed as clinically indicated. A marked QTc prolongation episode was defined as a QTc interval  $> 500$  ms, a threshold known to increase the risk of life-threatening cardiac events, and to predict short-term mortality independent of comorbidity [3].

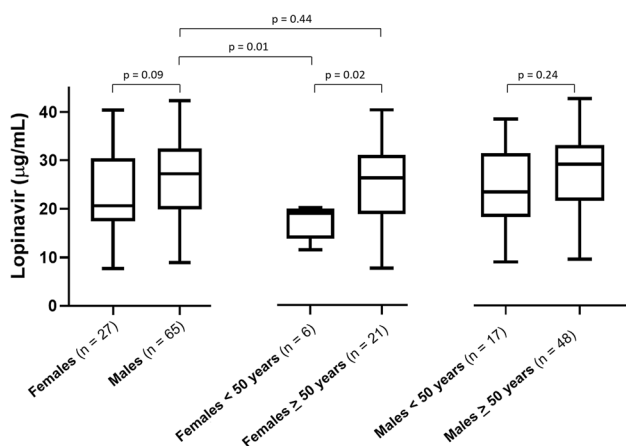
The study population consisted of 92 patients with COVID-19, of those 65 (71%) were male and 27 (29%) were female [2]. Male and female patients had a median (interquartile range) age of 59 (47–70) and 59 (52–65) years, respectively. Clinical laboratory parameters were comparable in male and female patients. There was a trend towards higher median LPV trough concentrations in male compared with female patients (27.2 vs 20.6  $\mu\text{g/mL}$ ,  $p = 0.09$ ). When categorizing female patients by age group to reflect hormonal changes related to menopause, the median LPV trough concentrations were not different in female patients aged  $\geq 50$  years compared to male patients, irrespective of age (26.3 vs 27.2  $\mu\text{g/mL}$ ,  $p = 0.44$ ). However, female patients aged  $< 50$  years had significantly lower LPV concentrations compared with male patients (19.0 vs 27.2  $\mu\text{g/mL}$ ,  $p = 0.01$ ). Lopinavir concentrations were not significantly different in male patients aged  $< 50$  and  $\geq 50$  years (Fig. 1). Marked QTc prolongation episodes were not observed in patients aged  $< 50$  years ( $n = 23$ ). Among patients with COVID-19 aged  $\geq 50$  years and in the absence of an electrolyte imbalance or concomitant drug with a QT prolongation risk (other than LPV and HCQ), the proportion of patients with a QTc interval of  $\geq 500$  ms was approximately three times higher in male than in female patients (12.5% [6/48] vs 4.8% [1/21]). Furthermore, male patients had higher QTc prolongation intervals as indicated in Table 1. There were no events of torsade de pointes.

COVID-19 shows a sex disparity in its clinical outcome. While the number of male and female patients contracting

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**Fig. 1** Box plots (showing the 5th, 25th, 50th, 75th, and 95th percentiles) of lopinavir plasma trough concentrations according to sex. Female and male patients were further categorized by age < 50 years and  $\geq$  50 years

**Table 1** Actual corrected QT (QTc) values in seven study participants with marked QTc prolongation episodes

Sex	Age (years)	QTc (ms)
Male	77	525
Male	50	523
Male	60	503
Male	59	515
Male	81	523
Male	82	512
Female	52	507

ms milliseconds

COVID-19 appears to be similar, more severe disease and a higher mortality rate are observed in male compared with female patients, even after adjusting for coexisting comorbidities. The observed difference is likely related to biological determinants. The X-chromosome contains a high density of immune-related genes involved in both the innate and adaptive responses [4]. Female patients are less susceptible to many infections, and hence, have an immunological advantage over male patients [4]. This phenomenon has also been associated with less severe courses of viral infections in female patients. Hormones may explain the observed sex disparity in the course of COVID-19. Estradiol downregulates the angiotensin-converting enzyme 2 (ACE2), the entry receptor of SARS-CoV-2 [5]. Levels of estradiol were shown to be negatively correlated with the pro-inflammatory cytokine interleukin-6 (IL-6) [6]. Elevated IL-6 levels inhibit drug metabolism mediated by CYP3A4 resulting in high drug concentrations [2]. Furthermore, inflammatory cytokines increase the risk of QT interval prolongation and life-threatening arrhythmias owing to their electrophysiological effects on the myocardium [7]. These considerations led us to

hypothesize that male patients with COVID-19 are more likely to present with elevated drug plasma concentrations and cardiac adverse events. We demonstrated a sex difference in median LPV trough plasma concentrations, with concentrations 30% lower in female patients aged <50 years compared with male patients. This observation is in agreement with the fact that pre-menopausal female patients have high estradiol levels, lower IL-6 plasma levels [6], and consequently less inhibition of CYP3A4 metabolism and lower drug concentrations [2]. However, we were unable to investigate the precise menstruation cycle in our female COVID-19 patient population. Importantly, higher plasma concentrations of narrow therapeutic index drugs in male patients and post-menopausal female patients raise the concern of an increased risk of ADRs and a higher magnitude of drug–drug interactions with medications whose metabolism is inhibited by LPV/r [2]. Our analysis showed that male patients with COVID-19 were more likely to present with a marked prolongation of the QTc interval than female patients. This finding goes alongside the finding of Zekarias et al. [1].

In addition to the inhibition of CYP3A4 metabolism and the related high drug concentrations, ADR cascade, other factors may contribute to the observed frequency of a prolonged QT interval in male patients. High IL-6 levels in male patients lead to direct myocardial injury [7]. Furthermore, ACE2 is expressed both in the lung and heart tissues, thus downregulation of ACE2 by estradiol [5] may decrease the risk of cardiac inflammation and associated QT interval prolongation in female patients. Because of the immunomodulatory effect of estradiol, it has been suggested that the hormone per se or in combination with antivirals may represent a viable therapeutic option for COVID-19. Of interest, pre-menopausal female patients were shown to have a milder course of COVID-19, better outcomes, and shorter hospitalization times than menopausal female patients [6]. Estradiol is currently being evaluated in a clinical trial to reduce the severity of symptoms in patients with COVID-19 (NCT04359329).

**Acknowledgements** We thank all the healthcare professionals and personnel in our institution involved in organizational processes and patient care during the COVID-19 pandemic.

## Declarations

**Funding** Catia Marzolini was supported by the Adolf and Mary Mil foundation. Felix Stader was supported by a grant from the Swiss National Foundation (Grant Number: 324730\_188504). Anne Leuppi-Taegtmeier, Marcel Stoeckle, Manuel Battegay, and Parham Sendi conducted this study as part of their routine work.

**Conflict of interest** Catia Marzolini, Felix Stader, Anne Leuppi-Taegtmeier, Marcel Stoeckle, Manuel Battegay, and Parham Sendi have no conflicts of interest that are directly related to the content of this study.

**Consent to participate** The study was approved by the Northwest/Central Switzerland Ethics Committee (EKNZ 2020-00769).

**Consent for publication** Patient consent for publication is regulated within the approval by the ethics committee. All authors have read the final version of the manuscript and gave their consent for publication.

**Availability of Data and Material** The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request under the precondition of the rules and regulations stated by the Swiss Human Research Act.

**Authors' Contributions** CM had the study idea. CM, FS, and PS analyzed the data. ALT contributed to data generation and electrocardiogram monitoring. CM and PS wrote the first draft of the manuscript. CM, FS, ALT, MS, MB, and PS co-wrote the manuscript, revised the manuscript, and approved the final version.

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