Ineffective of lopinavir/ritonavir and chloroquine for a COVID-19 treatment: A perspective of physiologically-based pharmacokinetic and pharmacodynamic modelling

Teerachat Saeheng[1], Juntra Karbwang[1], and Kesara Na-Bangchang[2]

[1]Thammasat University
[2]Thammasat University (Rangsit Campus)

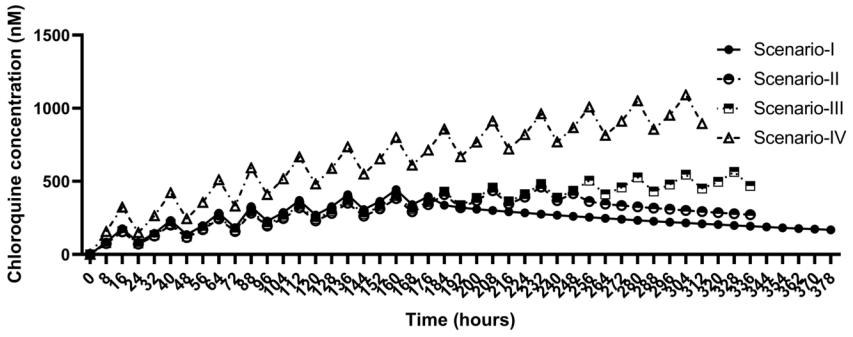
March 07, 2024

Abstract

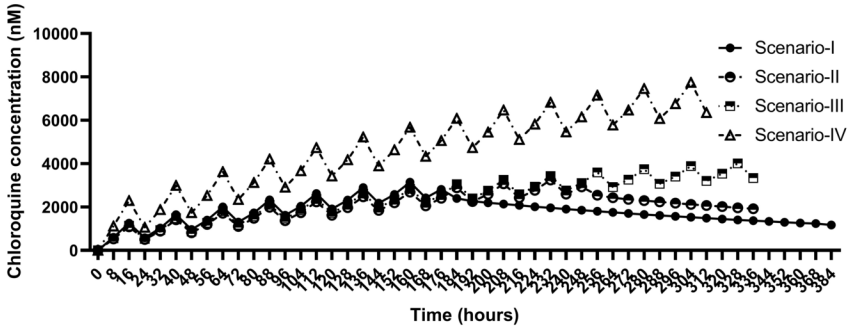
Ineffective selection of therapeutic drugs during an urgent situation leads to failure for COVID-19 treatment in large clinical trials, resulting in wasting time and cost. We aimed to demonstrate the utility of physiologically-based pharmacokinetic (PBPK)/pharmacodynamic (PD) modeling to support the withdrawal of chloroquine and ritonavir-boosted lopinavir (LPV/r) for COVID-19 treatment. The developed whole-body PBPK models were validated against clinical data. Model validation was performed using acceptable methods. The inhibitory effect was calculated to demonstrate drug efficacy. Various regimens of chloroquine and LPV/r for COVID-19 treatment in different clinical trials were used for a simulation. The risk of cardiotoxicity following high dose chloroquine administration was assessed. The effect of lung pH on drug concentrations in epithelial lining fluid (ELF) following a high dose of chloroquine and LPV/r was evaluated. The whole-body PBPK models were successfully developed (AAFEs of 1.2-fold). The inhibitory effect (%E) of chloroquine following high dose regimens in both ELF and bronchial epithelial cells (BEC) were lower than 2 and 1%, respectively. The corresponding values for the high dose of LPV/r were 40 and 2%, respectively. The risk of prolonged QTc in the population was higher than 20%. In addition, the %E of chloroquine was increased to 76% at pH 5.6 and decreased to 0.13% at pH 7.5. The change in pH in ELF had no influence on LPV/r concentrations. PBPK/PD modelling supports the withdrawal of chloroquine and LPV/r for COVID-19 treatment as an effective tool for the selection of therapeutic drug regimens in urgent situation.

Hosted file

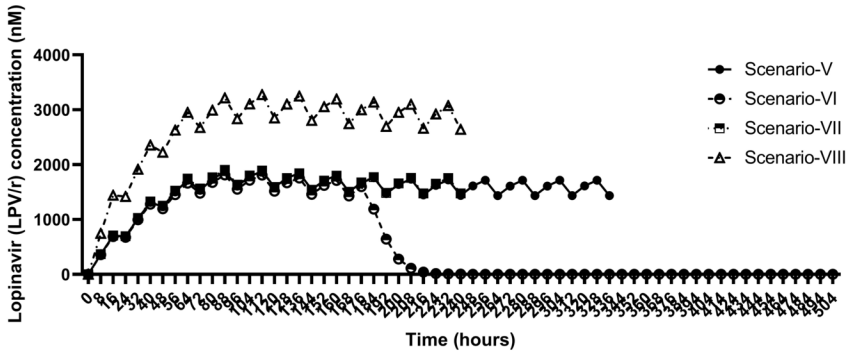
`TEERACHAT_PBPK_COVID19_VERSION_1.docx` available at https://authorea.com/users/172905/articles/713447-ineffective-of-lopinavir-ritonavir-and-chloroquine-for-a-covid-19-treatment-a-perspective-of-physiologically-based-pharmacokinetic-and-pharmacodynamic-modelling



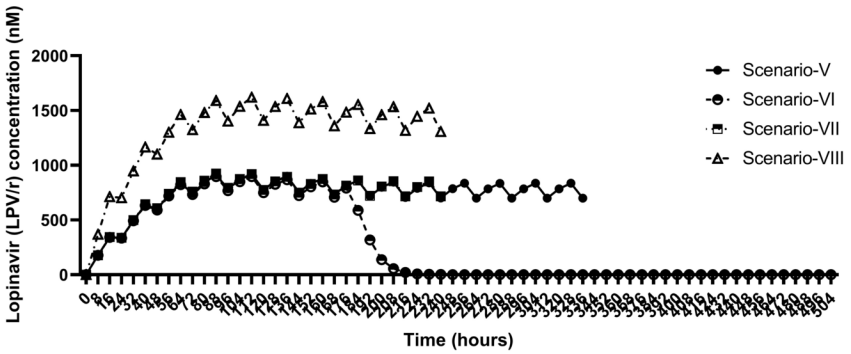
EC_{90} = 582300 nM.



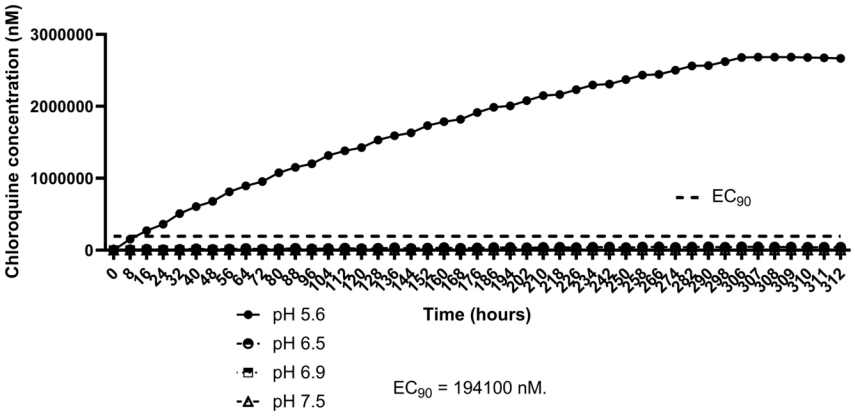
EC_{90} = 194000 nM.



EC_{90} = 65100 nM.



EC_{90} = 45300 nM.



EC_{90} = 194100 nM.

Hosted file

`Table [BJCP].docx` available at https://authorea.com/users/172905/articles/713447-ineffective-of-lopinavir-ritonavir-and-chloroquine-for-a-covid-19-treatment-a-perspective-of-physiologically-based-pharmacokinetic-and-pharmacodynamic-modelling