

Physiologically-based pharmacokinetic and pharmacodynamic (PBPK/PD) modeling as a tool for antiviral drug dose regimens for COVID-19

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Abstract

Background and Purpose: Ritonavir-boosted lopinavir and chloroquine were withdrawn for COVID-19 treatment according to WHO recommendation. However, lopinavir is still being used for COVID-19 treatment in a clinical practice guideline without supportive evidence. We demonstrated the utility of physiologically-based pharmacokinetic (PBPK)/pharmacodynamic (PD) models to support clinical use of lopinavir and the withdrawal of chloroquine for COVID-19 treatment. **Experimental approach:** The developed whole-body PBPK models were validated against clinical data. Model validation was performed using acceptable methods. The inhibitory effect (%E) was calculated to demonstrate drug efficacy. The recommended drug regimen for COVID-19 was the combination of 400/100 mg lopinavir/ritonavir given twice daily and 300 mg base chloroquine given twice daily for 14 days. **Key Results:** This study successfully developed whole-body PBPK models (AAFEs of 1.2-fold). For patients with a 70 kg body weight, %E for chloroquine in epithelial lining fluid (ELF) and bronchial epithelial cells (BEC) were about 2% and 12%, respectively. The corresponding values for lopinavir were 66% and 87.4%, respectively. With the increased body weight to 90 kg, %E for lopinavir in BEC dramatically dropped to lower than 60%, while that in ELF was slightly decreased (86.87%). **Conclusion and Implications:** The results support the decision of withdrawing chloroquine and using lopinavir in asymptomatic (with positive antigen kit test) or mild COVID-19 cases. In addition, results support the administration of antiviral drugs within the ten days of infection to prevent treatment failure.

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