Abstract of Dissertation submitted by SAE-HENG TEERACHAT

Physiologically-Based Pharmacokinetic Modeling for Optimal Dosage Prediction of Quinine Coadministered With Ritonavir-Boosted Lopinavir

（生理学的薬物速度論を用いたキニンとリトナビル/ロピナビルの合剤を同時投与する時の適切量の同定）

Teerachat Saeheng, Kesara Na-Bangchang, Marco Siccardi, Rajith KR Rajoli, and Juntra Karbwang
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Department of Infection Research, Nagasaki University Graduate School of Biomedical Sciences
(Supervisor: Professor Juntra Karbwang)

Introduction:

Malaria is reported as the third frequent cause of HIV-related morbidity and mortality in African countries. The estimated number of HIV co-infected with malaria deaths was 65,000 in Africa every year. The malaria patients co-infected with HIVs are required to receive both antimalarial drugs, and antiretroviral drugs. The incidence and relevance of drug-drug interactions (DDIs) between the antimalarial drugs (victim) and antiretroviral drugs (perpetrator)have been increasing and unavoidable, resulting in impaired inefficacy of malarial treatment or increase its adverse effects. Previous two studies of quinine (antimalarial drug) with ritonavir-boosted lopinavir (antiretroviral drug) in healthy volunteers showed significant reduction of quinine concentrations. A threefold increase in quinine dosage was suggested to counteract with the effects of lopinavir/ritonavir. These two studies, however, were limited in healthy volunteers, and not repeated doses for treatment. In addition, patients with malaria have impaired physiologies compared to healthy volunteers e.g., jaundice (impaired hepatic functions), and chronic renal failure (impaired renal functions).

Traditional dosing strategy for dose adjustment is “trial and error” to find the optimal dose based on the clinical response. This strategy could result in inappropriate dose regimen, and thus, increase risk of toxicity, and/or treatment failure in patients. Physiologically-based pharmacokinetic (PBPK) modeling has been recognized as a reliable tool to predict optimal dosage in various situations (e.g., concomitant medication (DDIs), renal insufficiency, genetic polymorphisms, and hepatic insufficiency). The objective of the study was to apply physiologically-based pharmacokinetic (PBPK) modeling to predict optimal dosage regimens of quinine when co-administered with lopinavir/ritonavir in malaria and HIV co-infected patients in the following conditions: (i) chronic renal failure, (ii) hepatic insufficiency, and (iii) CYP3A4 polymorphisms.

Materials and Methods:

The whole PBPK model was constructed for three drugs combination (quinine, ritonavir, and lopinavir) based on the previously published in formulation of ritonavir-boosted darunavir (DRV/r) using Simbiology version 5.8.2, a product of Matlab® version 2019a (MathWorks, Natick, MA).The physiochemical, biochemical properties of each drug for model construction were collected based on the published articles. The initial model assumptions were blood-flow limited model, immediate dissolution, no absorption from stomach, and large intestine, and no enterohepatic recirculation. The fraction of drug metabolism of CYP3A4, and UGT1A1 for quinine were assumed to be 0.44, and 0.56, respectively. There was no effect of 3-hydroxyquinine (quinine metabolite) on CYP3A4. The developed model was validated against literature. 100 virtual population aged between 18 to 60 years, and aged between 30 to 50 years were simulated for patients with malaria and HIVs co-infection and CYP3A4 polymorphisms (CYP3A4*3, CYP3A4*13, CYP3A4*18, and CYP3A4*19), and patients with malaria and HIVs co-infection with hepatic, and/or renal insufficiency, respectively. Model verification was evaluated using the most commonly accepted method (absolute average-folding errors or AAFEs). The acceptable ranges of AAFEs were within 2-fold. Sensitivity analysis (sensitivity coefficient) was performed to determine the effects of selected model input parameters on the Area Under Curve (AUC). Multiple doses of lopinavir/ritonavir (400/100 mg) given twice a day for 21 consecutive days (with co-administration of 600 mg quinine administration three times a day (T.I.D.)on day 14 for a 7-day course) were simulated in fasting state. The AUC ratio (AUCR) was calculated to determine the effect of lopinavir/ritonavir on quinine pharmacokinetics. The optimal dosage of quinine for curative malaria treatment was determined based on the unbound of quinine concentration reported in clinically published data i.e., unbound $AUC_{3\text{-}7days}$ > 2.18 mg/L/day, unbound peak plasma concentration (C_{max}) < 2.18 mg/L, and unbound trough plasma concentration (C_{trough}) ≥ 0.34 mg/L).

Result:

The AAFEs (ranges) for all model validation was 1.15-fold (1.02-1.27).The AAFEs (ranges) for all quinine prediction was 1.13-fold (1.02-1.27). Besides, the AAFEs (ranges) of quinine when co-administered with lopinavir/ritonavir was 1.16-fold (1.12-1.27). The AAFEs (ranges) of lopinavir as given as lopinavir/ritonavir

was 1.18-fold (1.18-1.23).All sensitivity coefficients were less than one, indicating that none of model input parameters has effect on model construction. The $AUC_{3\text{-}7days}$ and C_{trough} (±95% confidence interval or CI)in patients with malaria and HIVs co-infection based on standard dose regimen of quinine administration (648 mg T.I.D.) were 2.15 (2.07-2.23) mg/day/L, and 0.43 (0.41-0.44) mg/L, respectively. The AUCR was approximately 0.3. The suggested dose regimen was 1800 mg T.I.D. This regimen resulted in desired unbound $AUC_{3\text{-}7days}$, C_{trough}, and C_{max}. However, the average unbound $AUC_{3\text{-}7days}$ was relatively high. The dose regimen was decreased to 1200 mg T.I.D. The other doses including 2400 mg twice a day (B.I.D.), and 6000 mg once a day (Q.D.) were simulated and yielded the unbound $AUC_{3\text{-}7days}$, C_{trough}, and C_{max} within the set criteria. The average unbound $AUC_{3\text{-}7days}$, C_{trough}, and C_{max} for quinine co-administered with lopinavir/ritonavir based on the recommended standard dose regimen of quinine (a loading dose of 648 mg, followed by 324 mg B.I.D.) in renal failure without dialysis were within the reported therapeutic ranges. But the unbound C_{trough} concentrations were close to the cut-off criteria. The subsequent dose regimen i.e., 972 mg B.I.D. was simulated. However, the quinine 648 mg B.I.D. was considered adequate to provide the targeted therapeutic ranges. Based on the simulated results, the recommended dose of quinine administration (648 mg T.I.D.) when co-administered with lopinavir/ritonavir in all class of hepatic insufficiency except for severe hepatic insufficiency was enough to provide the desired unbound $AUC_{3\text{-}7days}$, C_{trough}, and C_{max}. The subsequent dose reduction (324 mg B.I.D.) in severe hepatic insufficiency was simulated. The AUCR in CYP3A4 polymorphisms ranged from 0.43 to 0.44 folds, the higher dose was required. Based on the standard dose regimen of quinine administration (648 mg T.I.D.), the unbound $AUC_{3\text{-}7days}$, C_{trough}, and C_{max}) were increased compared to a wild type, but within therapeutic ranges.

Discussion:

PBPK model successfully predicted quinine disposition in various clinical situations, including chronic renal failure without dialysis, and impaired liver function. The simulation of dose adjustment of unbound quinine suggested that 1200 mg or 1800 mg T.I.D., or 2400 mg B.I.D., or 6000 mg Q.D. represent suitable dosing strategies to overcome this DDIs. The 1200 mg T.I.D. is likely to be low too account for the large interindividual variability in quinine clearance and plasma concentrations. Once-daily dose regimen has been shown to improve patient compliance compared with the two times daily and three times daily dose regimens. The simulated unbound exposure for 2400 mg B.I.D. and 6000 mg Q.D. dose regimens could support better patient compliance, these dose regimens, however, would result in excessive number of tablets. The optimal dose of quinine when co-administered with lopinavir/ritonavir in chronic renal failure without dialysis was 648 mg B.I.D. The corresponding dose in hepatic insufficiency in all class except for severe hepatic insufficiency was 648 mg T.I.D., where the optimal dose quinine in severe hepatic insufficiency was 324 mg B.I.D. Our simulated results were in accordance with the product label of quinine, and Orlando and colleagues for no requirement of dose adjustment, but with continued monitoring of plasma quinine concentrations. The limitation of the current study in severe hepatic insufficiency is that data from a single-instead of repeat-dose administration were used for the study and ,therefore, therapeutic drug concentration was not achieved. The suggested optimal dose regimen for CYP3A4 polymorphisms was 648 mg T.I.D.