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Assessing the Impact of Antiretroviral Mediated Drug-Drug Interactions on Piperaquine Antimalarial Treatment in Pregnant Women Using Physiologically Based Pharmacokinetic Modelling

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Abstract : Introduction: Malaria in pregnancy has morbidity and mortality implication on both mother and unborn child. Piperaquine (PQ) based antimalarial treatment is emerging as a choice antimalarial for pregnant women in the face of resistance to current antimalarial treatment recommendation in pregnancy. Physiological and biochemical changes in pregnant women may affect the pharmacokinetics of the antimalarial drug in these. In malaria endemic regions other infectious diseases like HIV/AIDs are prevalent. Pregnant women who are co-infected with malaria and HIV/AID are at even more greater risk of death not only due to complications of the diseases but also due to drug-drug interactions (DDIs) between antimalarials (AMT) and antiretroviral (ARVs). In this study, physiologically based pharmacokinetic (PBPK) modelling was used to investigate the effect of physiological and biochemical changes on the impact of ARV mediated DDIs in pregnant women in three countries. Method: A PBPK model for PQ was developed on SimCYP® using published physicochemical and pharmacokinetic data of PQ from literature, this was validated in three customized population groups from Thailand, Sudan and Papua New Guinea with clinical data. Validation of PQ model was also done in presence of interaction with efavirenz (pre-validated on SimCYP®). Different albumin levels and pregnancy stages was simulated in the presence of interaction with standard doses of efavirenz and ritonavir. PQ day 7 concentration of 30ng/ml was used as the efficacy endpoint for PQ treatment.. Results: The median day 7 concentration of PQ remained virtually consistent throughout pregnancy and were satisfactory across the three population groups ranging from 26-34.1ng/ml; this implied the efficacy of PQ throughout pregnancy. DDI interaction with ritonavir and efavirenz resulted in modest effect on the day 7 concentrations of PQ with AUCratio ranging from 0.56-0.8 and 1.64-1.79 for efavirenz and ritonavir respectively over 10-40 gestational weeks, however, a reduction in human serum albumin level reflective of severe malaria resulted in significantly reduced the number of subjects attaining the PQ day 7 concentration in the presence of both DDIs. The model demonstrated that the DDI between PQ and ARV in pregnant women with different malaria severities can alter the pharmacokinetic of PQ.

Keywords : antiretroviral, malaria, piperaquine, pregnancy, physiologically-based pharmacokinetics
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