Population pharmacokinetics of rifabutin among co-infected children on lopinavir/ritonavir-based antiretroviral therapy

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Background

Drug-drug interactions make treating TB/HIV co-infection challenging. In adults, it is recommended to substitute rifampicin with rifabutin during lopinavir/ritonavir (LPV/r)-based antiretroviral therapy (ART) since rifabutin is a weak inducer of CYP3A4 and can be used with standard LPV/r. Rifabutin is metabolized by human-arylacetamide-deacetylase to 25-hydroxy-desacetyl-rifabutin (Des-rifabutin) and by CYP3A4 to other metabolites. Des-rifabutin is further metabolized by CYP3A4. Concomitant treatment with LPV/r increases exposures of rifabutin and des-rifabutin, through CYP3A4 inhibition. This could result in haematological toxicity. The aim of this analysis was to characterize rifabutin pharmacokinetics during LPV/r co-treatment.

Methods

Rifabutin and des-rifabutin concentrations were obtained from prospective studies in Nigerian children with HIV/TB co-infection in three age cohorts. An ≤3-yearold ART-naïve cohort received 15-20 mg/kg/day rifabutin for 2 weeks followed by initiation of LPV/r-based HIV treatment with a lower 2.5-5 mg/kg/day rifabutin dose. An older ART-experienced cohort received 2.5 mg/kg/day rifabutin from study inclusion. Rifabutin and 25-desacetyl-rifabutin concentrations were measured at 0, 2, 4, 8, 12, and 24-hours post-dose at weeks 2, 4, and 6 for the <1 year old, at weeks 2 and 4 for the 1-3 years old, and at weeks 2, 4, and 8 for the 3-15 years old cohorts. Data were analysed using nonlinear mixed effect modelling.

Results

34 participants with a median (range) age and weight of 31 (8-185) months and 11 (4.5-45) kg, respectively, were included. During LPV/r co-treatment, rifabutin bioavailability increased by 158% (95%CI:93.2%–246%), rifabutin CYP3A4-mediated clearance was inhibited, and des-rifabutin clearance was reduced by 76.6% (74.4%–78.3%). Severely malnourished children (ZWFA<-3) had a 26% (17.9%-33.7%) lower bioavailability.

Discussion/Conclusion

Concomitant administration of rifabutin and LPV/r increased systemic rifabutin and 25-desacetyl-rifabutin exposure, through increasing bioavailability and decreasing 25-desacetyl-rifabutin clearance, likely due to CYP3A4 inhibition. While rifabutin levels are adjusted for the interaction, the 25-desacetyl-rifabutin is higher with LPV/r, thus potentially increasing the risk of lowered neutrophil count. The model will be used to optimize rifabutin dose and to investigate safety of higher 25-desacetyl-rifabutin concentrations when cotreating.