Background: Tuberculosis patients with HIV infection often require lopinavir/ritonavir (co-formulated in 4:1 ratio; LPV/r)-based antiretroviral treatment with rifampicin-based antitubercular treatment. Rifampicin, a key component of antitubercular treatment, profoundly reduces lopinavir concentrations. Among adults, the amount of LPV/r has been shown to overcome this effect.

Objectives: To develop an integrated population pharmacokinetic model accounting for the drug-drug interactions between lopinavir, ritonavir and rifampicin, and to evaluate optimal dose of LPV/r when co-administered with rifampicin.

Methods

Steady state pharmacokinetics of lopinavir and ritonavir were evaluated in a cohort of 21 HIV-infected South African adults. The study design (Figure 1) was previously reported by Decloedt et al. Four sequential dose regimens were used and intensive pharmacokinetic sampling was performed at the end of each period. Patients took a meal before the evening dose, but fasted for 10 h for the morning dose. A population pharmacokinetic analysis was conducted using NONMEM 7.

Results

- Lopinavir was described by one-compartment with first order absorption model
- Ritonavir was described by two-compartment with transit absorption model
- Allometric scaling of oral clearance by fat free mass (FFM) and of volume of distribution by body weight (BW), for both drugs
- Dynamic inhibition of ritonavir concentrations on the oral clearance of lopinavir was modeled as an Emax model (Figure 2 and 3)
- Rifampicin treatment - reduces the bioavailability 20.2% for lopinavir and 45.0% for ritonavir - increases the oral clearance 71.0% for lopinavir and 36.0% for ritonavir
- Diurnal variation was investigated

For the evening dose (with meal and not fasted) and night profile:
- the bioavailability increased by 42.0% for lopinavir and 45.0% for ritonavir
- the oral clearance of both drugs decreased by 32.7%

Conclusions

- A population pharmacokinetic model was developed to simultaneously capture the drug-drug interactions between lopinavir, ritonavir and rifampicin.
- The model can be used to simulate alternative dosage regimens when lopinavir/ritonavir is co-administered with rifampicin.
- Doubling the dose of LPV/r is required in most patients to maintain lopinavir concentrations > 1 mg/L during rifampicin-based antitubercular treatment.
- The higher morning trough concentrations were explained by both higher bioavailability with the evening meal and lower clearance overnight, possibly due to reduced hepatic blood flow. However, more evidence is needed to confirm this.

Acknowledgments

Our study was funded by the European and Developing Countries Clinical Trials Partnership (EDCTP). CZ and PO were funded by the Wellcome Trust Programme Grant (083851/Z/07/Z). ED received partial support from the Fogarty International Centre/USNIH (U2RTW007370/3, 5U2RTW007373). We would like to acknowledge the staff and patients from the Hannan Crusaid Treatment Centre who enthusiastically participated in the study.