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Drug Interactions

The pharmacokinetics of Lopinavir in South African HIV-infected volunteers receiving rifampicin with adjusted doses of Lopinavir/ritonavir.

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Background: Rifampicin co-administration dramatically reduces plasma lopinavir concentrations. Doubling the dose of the capsule formulation of lopinavir/ritonavir (LPV/r) overcame this interaction in a healthy volunteer study. However, a subsequent study in healthy volunteers receiving the tablet formulation of LPV/r was stopped early due to high rates of hepatotoxicity, possibly due to the sequence of administration (rifampicin was started first) or not escalating the LPV/r dose gradually. We evaluated the steady state pharmacokinetics of LPV in HIV-infected adults virologically suppressed on a LPV/r regimen who were given rifampicin and the dose of LPV/r gradually increased.

Materials & Methods: Steady state pharmacokinetics of LPV was evaluated at baseline in a cohort of HIV-infected adults virologically suppressed on a LPV/r regimen (400 mg/100 mg 12 hourly of the tablet formulation). Rifampicin 600mg daily was commenced and after a week the LPV/r dose was increased 1.5 times (600 mg/150 mg 12 hourly); after another week the dose of LPV/r was doubled (800 mg/200 mg 12 hourly). Intense pharmacokinetic sampling was done after each dose adjustment. Safety assessments were conducted throughout the study: liver enzymes were measured and symptoms assessed at least twice weekly.

Results: 21 participants, of which 18 were female, were enrolled. The median (IQR) age was 36 (31-38) yrs and the mean (SD) CD4-count was 543±216 cells/mm3. The median (IQR) 12 hour LPV concentration (C12) was 4.3 (3.5-6.5) mg/L at baseline; 0.2 (0.1-0.5) mg/L after 7 days of rifampicin; 1.7 (0.14-4.4) mg/L with 1.5 times the dose of LPV/r; and 3.7 (1.2-7.7) mg/L with double dose LPV/r. There were no significant differences in LPV AUC12, C0, C12 and Cmax between the baseline and double dose LPV/r time points. Treatment was generally well tolerated with two participants developing asymptomatic grade 3/4 alanine aminotransferase elevation.

Conclusion: Doubling the dose of the tablet formulation of LPV/r overcomes the induction of rifampicin. Less hepatotoxicity occurred in our cohort of HIV-infected participants compared with those reported in healthy normal volunteer studies.

Conflict of interest
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