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Interaction studies of tipranavir-ritonavir with clarithromycin, fluconazole, and rifabutin in healthy volunteers.

la Porte CJ, Sabo JP, Elgadi M, Cameron DW.

Division of Infectious Diseases, Ottawa Hospital and Ottawa Health Research Institute, University of Ottawa, Ottawa, Canada. claporte@ohri.ca

Abstract

Three separate controlled, two-period studies with healthy volunteers assessed the pharmacokinetic interactions between tipranavir-ritonavir (TPV/r) in a 500/200-mg dose and 500 mg of clarithromycin (CLR), 100 mg of fluconazole (FCZ), or 150 mg of rifabutin (RFB). The CLR study was conducted with 24 subjects. The geometric mean ratios (GMR) and 90% confidence intervals (90% CI; given in parentheses) of the areas under the concentration-time curve (AUC), the maximum concentrations of the drugs in serum (C(max)), and the concentrations in serum at 12 h postdose (Cp12h) for multiple-dose TPV/r and multiple-dose CLR, indicating the effect of TPV/r on the CLR parameters, were 1.19 (1.04-1.37), 0.95 (0.83-1.09), and 1.68 (1.42-1.98), respectively. The formation of the metabolite 14-OH-CLR was decreased by 95% in the presence of TPV, and the TPV AUC increased 66% compared to that for human immunodeficiency virus (HIV)-negative historical controls. The FCZ study was conducted with 20 subjects. The GMR (and 90% CI) of the AUC, C(max), and Cp24h, indicating the effect of multiple-dose TPV/r on the multiple-dose FCZ parameters, were 0.92 (0.88-0.95), 0.94 (0.91-0.98), and 0.89 (0.85-0.92), respectively. The TPV AUC increased by 50% compared to that for HIV-negative historical controls. The RFB study was conducted with 24 subjects. The GMR (and 90% CI) of the AUC, C(max), and Cp12h for multiple-dose TPV/r and single-dose RFB, indicating the effect of TPV/r on the RFB parameters, were 2.90 (2.59-3.26), 1.70 (1.49-1.94), and 2.14 (1.90-2.41), respectively. The GMR (and 90% CI) of the AUC, C(max), and Cp12h of TPV/r and RFB with 25-O-desacetyl-RFB were 4.33 (3.86-4.86), 1.86 (1.63-2.12), and 2.76 (2.44-3.12), respectively. Coadministration of TPV with a single dose of RFB resulted in a 16% increase in the TPV Cp12h compared to that for TPV alone. In the general population, no dose adjustments are necessary for the combination of TPV/r and CLR or FCZ. Combining TPV/r with RFB should be done with caution, while toxicity and RFB drug levels should be monitored. Study medications were generally well-tolerated in these studies.

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