**Introduction**

ETR is a next-generation NNRTI with demonstrated activity in treatment-experienced HIV-infected patients, including those with NNRTI resistance. ETR is a substrate and inducer of CYP3A and a substrate and inhibitor of CYP2C9 and CYP2C19. In vitro, ETR is not a substrate, but an inhibitor of P-glycoprotein (P-gp) with a 50% inhibitory concentration (IC₅₀) of 24.2nM (10.5μg/mL). Digoxin is mainly eliminated renally as unchanged drug and is a substrate for P-gp. This study evaluated the effect of steady-state ETR on P-gp in HIV-negative volunteers, using digoxin as a probe.

**Methods**

In an open-label, randomized, two-period crossover trial a single oral dose of 0.5mg digoxin was administrated in Treatment A. After 14 days washout, 200mg ETR bid was administered for 12 days with a single oral dose of 0.5mg digoxin coadministered on Day 8 (Treatment B). Digoxin plasma concentrations were assessed over 120 hours after drug intake in Treatment A and on Day 8 of Treatment B. Pharmacokinetics of ETR were assessed over 12 hours after drug intake on Day 8 of Treatment B. Pharmacokinetic (PK) parameters were obtained by noncompartmental analysis and a linear mixed effects model was used for statistical analysis. Safety and tolerability were assessed throughout the trial.

**Results**

Sixteen male volunteers participated. Coadministration of digoxin with ETR resulted in higher mean plasma concentrations of digoxin in the first 2 hours after drug administration. Least squares (LS) means ratios (90% confidence interval [CI]) for digoxin maximum plasma concentration (Cmax) and area under the curve (AUC) were comparable to historical controls. No change in the urinary excretion of digoxin was observed. ETR mean Cmax and AUC were comparable to historical controls. The most frequently reported adverse event (AE) was headache (in five volunteers). One volunteer prematurely discontinued the trial due to viral bronchitis during Treatment B. No grade 3 or 4 AEs were reported. The coadministration of ETR and digoxin was generally safe and well tolerated.

**Conclusions**

Based on the increased plasma concentrations of digoxin when coadministered with ETR, a weak inhibitory effect of ETR on P-gp was observed. Clinically relevant interactions due to inhibition of P-gp are not anticipated. Digoxin can be coadministered with ETR without a priori dose adjustments. Standard monitoring of digoxin plasma concentrations is recommended.

**References**

2. INTELENCE™ package insert.

**Acknowledgments**

The authors would like to express their gratitude to the volunteers. We also acknowledge:

- PIF Research ([Pharmaceutical Research and Development] Berna, Belgium)
- Doeven [Department of Aneasthesiology and Critical Care Medicine, Aalst, Belgium]

**Abstract**

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