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No clinically relevant effect of etravirine (ETR; TMC125) on digoxin pharmacokinetics in HIV-negative volunteers

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Abstract

Background

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 (IC_{50}) of 24.2mM (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 administered 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 and urine pharmacokinetics 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 (C_{max}) and area under the curve from administration until the last timepoint with a measurable concentration after dosing (AUC_{last}), when coadministered with ETR, were 1.19 (0.96–1.49) and 1.18 (0.90–1.56), respectively, compared to administration alone. No change in the urinary excretion of digoxin was observed. ETR mean C_{max} and AUC_{12h} 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.

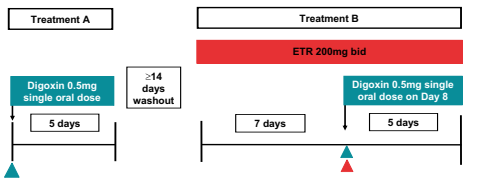
Introduction

- ETR is a next-generation NNRTI with potent in-vitro activity against both wild-type and NNRTI-resistant HIV-1[1,2]
- Two Phase III trials (DUET-1 and DUET-2 [TMC125-C206 and C216]) demonstrated significant antiviral benefit after 48 weeks of treatment with ETR in treatment-experienced patients with NNRTI resistance. Except for a higher incidence of rash, patients treated with ETR had an AE profile similar to placebo[3,4]
- ETR is a substrate and inducer of CYP3A4 and a substrate and inhibitor of CYP2C9 and CYP2C19. *In vitro*, ETR is not a substrate, but an inhibitor of P-gp with an IC_{50} of 24.2mM (10.5μg/mL)
- Digoxin is mainly eliminated renally as unchanged drug and it is a substrate for P-gp
- In order to assess the effect of ETR on P-gp, a drug–drug interaction study was conducted using digoxin as a probe

Study design

- TMC125-C180 was a Phase I, open-label, one-way, two-period crossover trial in 16 HIV-negative volunteers
- Two treatment sessions (A and B) were scheduled for all volunteers, separated by a washout period of at least 14 days as shown in the study design scheme. Half of the volunteers were randomized to start with Treatment A and the other half were randomized to start with Treatment B
- A single oral dose of digoxin 0.5mg was administered on Day 1 of Treatment A and Day 8 of Treatment B
- ETR was administered as 200mg bid for 12 days in Treatment B; all doses were taken within 10 minutes after a standardized meal
- Post-treatment safety visits took place 7 days and 31 (± 1) days after the last intake of trial medication
- The trial protocol was reviewed and approved by the appropriate institutional ethics committee and health authorities; the trial was conducted in accordance with the Declaration of Helsinki

Study design (cont'd)



▲ 120-hour PK analysis of digoxin in plasma and urine, determined on Day 1 of Treatment A and Day 8 of Treatment B
▲ 12-hour PK analysis of ETR on Day 8 of Treatment B

- Safety and tolerability assessments were performed throughout the trial until at least 30 days after the last trial medication intake

PK analyses

- Plasma concentrations of ETR were determined using a validated LC-MS/MS method (LLOQ 2ng/mL)
- Plasma and urine concentrations of digoxin were determined using a validated LC-MS/MS method (LLOQ 0.100ng/mL)
- PK and statistical PK analyses were performed using
  - WinNonLin Professional, version 4.1 (Pharsight Corporation, Mountain View, California, USA) and SAS System for Windows® version 9.1.3 (SAS Institute Inc., Cary, NC, USA)
  - a noncompartmental model with extravascular input was used for the PK analysis

LC-MS/MS = liquid chromatography-tandem mass spectrometry
LLOQ = lower limit of quantification

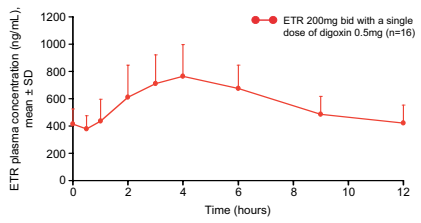
PK and safety parameters and statistical analyses

- Primary PK parameters
  - C_{max} (ng/mL)
  - AUC_{last} (ng•h/mL)
  - AUC_{∞} (ng•h/mL)
- Pharmacogenetic assessments of the MDR1 gene
  - Exon 26 (3435C>T)
  - Exon 21 (2677G>T,A)
- Safety parameters
  - AEs, laboratory assessments, electrocardiogram (ECG), vital signs assessment and physical examinations were performed throughout the study
  - severity and drug relationship of AEs to ETR and/or digoxin were recorded
- Statistical analyses
  - descriptive statistics were calculated for the PK parameters of digoxin and ETR
  - LS means ratios and 90% CIs were estimated with a linear mixed effects model
  - safety parameters were evaluated by descriptive statistics and frequency tabulations

Demographics

Demographic parameter	All volunteers (n=16)
Age, years, median (range)	32 (18–46)
Height, cm, median (range)	182 (173–194)
Weight, kg, median (range)	79 (59–97)
Body mass index, kg/m², median (range)	24 (18–29)
Male gender, n (%)	16 (100)
Ethnic origin, n (%)	
Caucasian	16 (100)

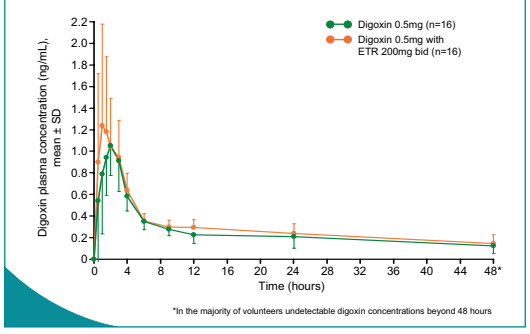
ETR pharmacokinetics



- PK parameters (mean ± SD)
  - C_{min} 353 ± 93ng/mL
  - C_{max} 822 ± 225ng/mL
  - AUC_{12h} 6856 ± 1680ng•h/mL

SD = standard deviation

Digoxin plasma PK profile



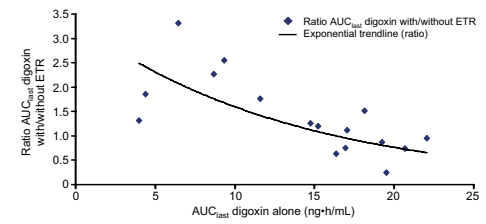
*In the majority of volunteers undetectable digoxin concentrations beyond 48 hours

Digoxin PK parameters

PK parameter	Digoxin alone (reference) (mean ± SD) (n=16)	Digoxin + ETR (test) (mean ± SD) (n=16)	LS mean ratio (test/reference) (90% CI)
C_{max} (ng/mL)	1.31 ± 0.36	1.63 ± 0.68	1.19 (0.96–1.49)
AUC_{last} (ng•h/mL)	14.03 ± 5.86	16.41 ± 6.52	1.18 (0.90–1.56)
AUC_{∞} (ng•h/mL)	21.72 ± 7.93	24.79 ± 7.98	NA
AE_{total} (mg)	0.14 ± 0.04	0.13 ± 0.03	NA
$D_{urine,total}$ (%)	26.97 ± 7.32	25.48 ± 6.19	NA

NA = not assessed

Digoxin PK parameters (cont'd)



- A trend of little to no effect of ETR on digoxin pharmacokinetics was observed in volunteers with higher exposure to digoxin when given alone
- No association was found between digoxin PK parameters and the genotypes for exons 21 or 26, nor with their haplotype combinations (data not shown)

Safety summary

- No serious AEs were reported
- The most frequently reported AE was grade 1 or 2 headache in four volunteers during ETR treatment and in five volunteers when ETR was coadministered with digoxin
- All AEs reported were mild (grade 1) or moderate (grade 2) in severity
- One volunteer discontinued the trial on Day 11 of Treatment B (ETR coadministered with digoxin) due to a grade 2 viral bronchitis
- One volunteer developed a grade 1 rash on Day 5 of Treatment B (ETR alone), possibly related to ETR, which spontaneously resolved before the end of the trial with continued dosing
- There were no consistent or relevant changes in laboratory or cardiovascular safety parameters or physical examinations

Conclusions

- When coadministered with ETR, digoxin C_{max} and AUC_{last} were increased by 19% and 18%, respectively; urinary excretion of digoxin was unchanged.
- Short-term coadministration of ETR with digoxin in HIV-negative volunteers was generally safe and well tolerated.
- ETR showed a weak inhibitory effect on P-gp; this is not expected to cause clinically relevant interactions with substrates for this transporter.
- Digoxin can be coadministered with ETR without *a priori* dose adjustments; however, standard monitoring of digoxin plasma concentrations is recommended.

References

1. Vingerhoets J, et al. J Virol 2005;79:12773–82.
2. INTELENCE™ package insert.
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4. Johnson M, et al. CROI 2008. Poster 791.

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This poster is available on-line at www.tibotec.com