Pharmacokinetic interaction between etravirine and fluconazole or voriconazole in HIV-negative volunteers

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Abstract

Background

Etravirine (ETR; TMC125) is a next-generation NNRTI with demonstrated activity in treatment-experienced, HIV-infected patients. ETR is a substrate and inducer of cytochrome P450 (CYP) CYP3A and a substrate and inhibitor of CYP2C9 and CYP2C19. Fluconazole (FLU) and voriconazole (VOR) are inhibitors of CYP3A, 2C9 and 2C19. This study evaluated the pharmacokinetics of ETR and FLU or VOR when co-administered.

Methods

In an open-label, randomized, two-way, three-period crossover trial, 200mg ETR bid was given for 8 days (Treatment A). In Treatments B and C, 200mg FLU qd or 200mg VOR bid, respectively, was administered for 16 days with 14-day washout periods. ETR 200mg bid was co-administered during Days 8–16. ETR pharmacokinetics were assessed on Day 8 of Treatment A and Day 16 of Treatments B and C; FLU and VOR pharmacokinetics on Days 8 and 16 of Treatments B and C, respectively. Pharmacokinetics (PK) parameters were calculated by non-compartmental analysis. Safety and tolerability were assessed.

Results

Eighteen volunteers participated (median age 29 years; three females). PK results are given below.

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>FLU with/without ETR (n=16)</th>
<th>VOR with/without ETR (n=14)</th>
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<tbody>
<tr>
<td>Cmin</td>
<td>2.09 (1.90–2.31)</td>
<td>1.23 (0.87–1.75)</td>
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<tr>
<td>Cmax</td>
<td>1.75 (1.60–1.91)</td>
<td>0.95 (0.75–1.21)</td>
</tr>
<tr>
<td>AUC12h/24h</td>
<td>1.86 (1.73–2.00)</td>
<td>1.14 (0.88–1.47)</td>
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</table>

LSM = least square means; CI = confidence interval; Cmin = minimum plasma concentration; Cmax = maximum plasma concentration; AUC12h/24h = area under the plasma concentration-time curve from time of administration to 12/24 hours after dosing.

Three volunteers withdrew consent, one discontinued due to leucocyturia when taking FLU alone. The most frequent adverse events (AEs) were headache and blurred vision (11 and eight volunteers, respectively) during VOR alone treatment. No grade 3 AEs were observed during the treatments.

Conclusions

Co-administration of ETR with FLU or VOR resulted in an increase of ETR steady-state concentrations. FLU pharmacokinetics were unchanged and VOR pharmacokinetics were slightly increased when given with ETR, all at steady-state. Combinations of ETR and FLU or VOR were generally safe and well tolerated.

Conclusions

- When co-administered with FLU or VOR, ETR steady-state plasma concentrations were increased
  - post-hoc analysis of AEs in DUET-1 and DUET-2 over 96 weeks in patients with and without co-administration of FLU showed no difference in safety profile (data on file)
- ETR had no effect on the pharmacokinetics of FLU when these two drugs were co-administered at steady-state
- VOR pharmacokinetics were slightly increased when co-administered with ETR; no increase was observed in carriers of CYP2C19 *2 allele
- Co-administration of ETR with FLU or VOR in HIV-negative volunteers was generally safe and well tolerated.

References


Acknowledgments

The authors would like to express their gratitude to the volunteers. They also acknowledge
- V Millenium, JH Pharmaceutical Research and Development, Beerse, Belgium
- P Kalawage, Kendle Clinical Pharmacology Unit, Utrecht, The Netherlands

Editorial support provided by Gardiner-Caldwell Communications; this support was funded by Tibotec.