AVOID SIMULTANEOUS PRESCRIPTION BETWEEN LINEZOLID AND VORICONAZOL: PHARMACOKINETIC STUDY

Idoate Grijalba AI, Leache Alegría L, Aldaz Pastor A
Pharmacy Department. University Clinic of Navarra. Pamplona.

Introduction

Take linezolid (LIN) and voriconazole (VCZ) at same time is common in routine clinical practice.


Linezolid (LIN): Metabolized in two metabolites (65%). Main metabolite independent of cytochrome P-450-isoenzymes

Objective: Analyze the potential of interaction between LIN and VCZ by pharmacokinetic monitoring.

Material y Methods

• Single-centre, retrospective and observational study.
• Patients under simultaneous treatment with LIN and VCZ between March-2009 to December-2015

1. Serum samples were drawn
2. Liquid chromatography (HPLC)
3. Plasma concentrations of VCZ
   • Before treatment with LIN
   • After at least 3 days of combined therapy.
4. Oral apparent VCZ clearance (CL/F L/h) was estimated
   • Before treatment with LIN (CL/Fb)
   • During LIN treatment (CL/Fd LIN)

Variables

✓ Demographic: age, sex
✓ Treatment: dosing schedule, date and time of each dose.
✓ Clinic: diagnosis, microbiological information, etc.
✓ Kinetics: date and time of each sample

Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ( men %)</td>
<td>100%</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>67(57-73)</td>
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<tr>
<td>Dose/day LIN (mg)</td>
<td>1.200</td>
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<tr>
<td>Dose/day VCZ (mg), mean ± SD</td>
<td>454.5±157.2</td>
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<tr>
<td>CL/Fb (L/h)</td>
<td>2.7±0.8</td>
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<tr>
<td>CL/Fd LIN (L/h)</td>
<td>22.1±11.7</td>
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80% (n=4) Infra-therapeutic VCZ concentrations

20% (n=1) Ultrarrapid metabolizer (CYP2C19*27*27) had infra-therapeutic concentrations before combined therapy VCZ-LIN

Probable Interaction VCZ-LIN

3 change anti-infective treatment to vancomycin or daptomycin.

2 Maintained linezolid and increase VCZ dose up to 75% to reach at least the lower limit of therapeutic range.

Conclusion

✓ Add LIN to VCZ treatment increases VCZ clearance between 250-700% and as a result, plasma antifungal concentrations decrease with a significant clinical effect. This translates into a loss of effectiveness in antifungal treatment in 80% of cases.
✓ The use of this combination is contraindicated and if clinically there is no other alternative, VCZ pharmacokinetic monitoring is recommended to ensure effectiveness of antifungal treatment.

Therapeutic range of VCZ

Candida spp.: 1.5 – 4.5 mcg/mL
Aspergillus spp.: 2 – 4.5 mcg/mL

VCZ concentrations observed (mcg/mL): 0.9, 0.93, 0.42, 1.13, 1.21
VCZ concentrations target (mcg/mL): 2-5