BACKGROUND: Solithromycin is a novel fourth generation macrolide fluoroketolide antibiotic undergoing Phase 3 trials in adults. Phase 1 studies in children and infants are planned and dried blood spot (DBS) samples can minimize blood sample volumes.

METHODS: We enrolled adolescents with suspected or confirmed bacterial infections who received solithromycin capsules (12 mg/kg on Day 1 [up to 800 mg], and 6 mg/kg daily on Days 2-5 [up to 400 mg]). We collected paired DBS-plasma samples at pre-specified sampling points. Data for this analysis were available September 30, 2014. We used weighted linear regression (WLR) and DBS/plasma concentration ratio to perform a comparability analysis.

RESULTS: 12 adolescents (median age 16 years [range; 12-17]; weight 64 kg [30-84]; 75% male) had 92 paired DBS-plasma samples available for analysis. We observed a linear relationship between DBS and plasma concentrations, slope=0.91 (95% CI: 0.82, 0.99). The mean DBS/plasma concentration ratio was 0.96 (95% CI: 0.89, 1.04) and was conserved throughout the concentration range, ratio slope=0.0006 (95% CI:0.0002, 0.0001).

CONCLUSION: DBS and plasma solithromycin concentrations were comparable in a small cohort of adolescents. The results are promising and further validation of this method is warranted.

Materials and Methods

We performed a phase 1 clinical trial in adolescents with suspected or confirmed infections.

Adolescents received solithromycin 12 mg/kg (up to 800 mg, adult maximum) on Day 1 and 6 mg/kg (up to 400 mg, adult maximum) on Days 2-5 as add-on therapy.

We collected paired plasma-DBS PK samples at 0.5–1.5, 2–4, 8–10, and 23–24 hours on the first and last day of dosing.

We collected DBS samples on Whatman® FTA® DMPK Type C cards (20 μL).

PK samples were analyzed by a centralized laboratory using a validated LC/MS/MS method.

We used weighted linear regression and the DBS/plasma concentration ratio to compare solithromycin concentrations in plasma and DBS samples.

SoliThromycin Concentrations Measured in Dried Blood Spots Collected from Adolescents

Table 1. Clinical data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (range) or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>12</td>
</tr>
<tr>
<td>Paired samples</td>
<td>92</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>800 (400-800)</td>
</tr>
<tr>
<td>Day 1</td>
<td>800 (400-800)</td>
</tr>
<tr>
<td>Days 2–5</td>
<td>400 (200-400)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>16 (12–17)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64 (30–84)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>38 (22–45)</td>
</tr>
<tr>
<td>Male sex</td>
<td>9 (75%)</td>
</tr>
</tbody>
</table>

Results

The mean difference (95% CI) in DBS and plasma sample CEM101 concentrations was 57.20 ng/mL (8.30, 106.09) and the limits of agreement (reference range for difference, ±2 SD) were -415.01 ng/mL to 529.40 ng/mL.

The mean DBS/plasma concentration ratio was 0.96 (95% CI: 0.89, 1.04) and was conserved throughout the concentration range, ratio slope=0.0006 (95% CI:0.0002, 0.0001).

Conclusions

- On average, DBS and plasma solithromycin concentrations were comparable in a small cohort of adolescents, however there was substantial variability in the range of the DBS/plasma ratio.
- A slope near unity indicates that significant red blood cell partitioning occurs, which is in agreement with previously observed data (~75% whole blood: plasma partitioning based on total radioactivity).
- Additional data are needed to determine the utility of solithromycin DBS concentrations in future clinical trials.

Acknowledgements

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- The authors would like to acknowledge Dr. Elle Swift, MD for the contributions to the study.

Figure 1. Dried blood spot solithromycin concentration (ng/mL) vs. plasma solithromycin concentration (ng/mL).

Figure 2. Sample type vs. plasma solithromycin concentrations.

Figure 3. Solithromycin DBS/plasma ratio vs. plasma concentration.

Table 1. Clinical data.