

Solothromycin Concentrations Measured in Dried Blood Spots Collected from Adolescents

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Abstract

BACKGROUND: Solithromycin is a new 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.

Introduction

- Solithromycin is a fluoroketolide antibiotic with activity against a wide array of respiratory tract and other pathogens.
- Positive results were observed in a global, phase 3 clinical trial in adults with community-acquired bacterial pneumonia (CABP).
- Pediatric studies are ongoing and will involve infants <2 years of age, who will benefit from small PK sample volumes.
- DBS sampling is a novel drug sampling technique that has numerous advantages over traditional methods: significantly reduced blood volumes (10–25 μ L), reduced biohazard risk, ease of storage (room temperature), and improved drug stability.
- The use of DBS PK sampling has not been validated for solithromycin.

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.
- DBS samples were collected on Whatman® FTA® DMPK Type C cards (20 μ L).
- PK samples were analyzed by a central 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.

Results

Table 1. Clinical data.

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

- Mean (SD) solithromycin concentrations were 392.1 (434.32) and 449.3 (525.56) ng/mL in DBS and plasma, respectively (P =0.05).

Figure 1. Solithromycin concentration versus time in both matrices.

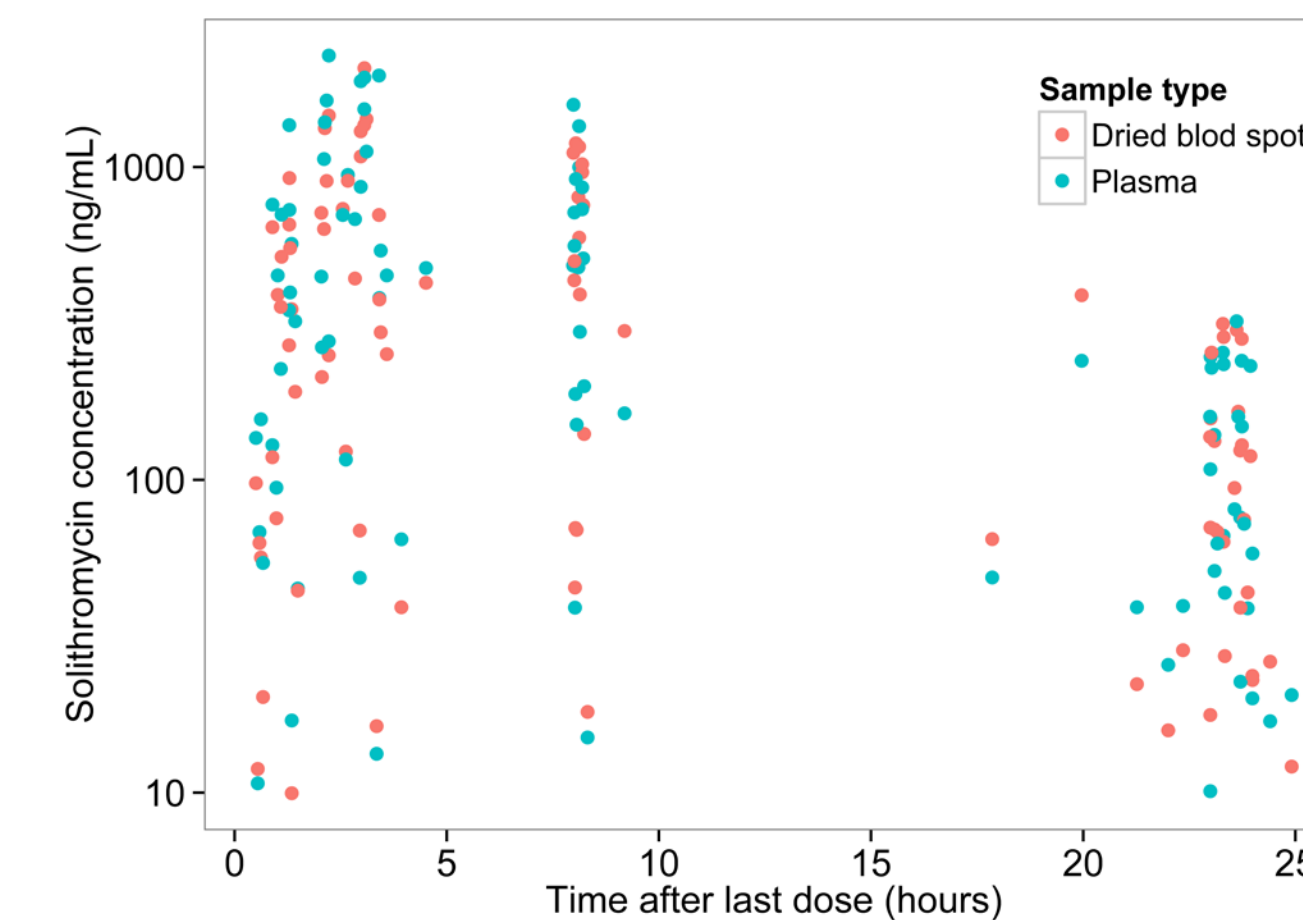
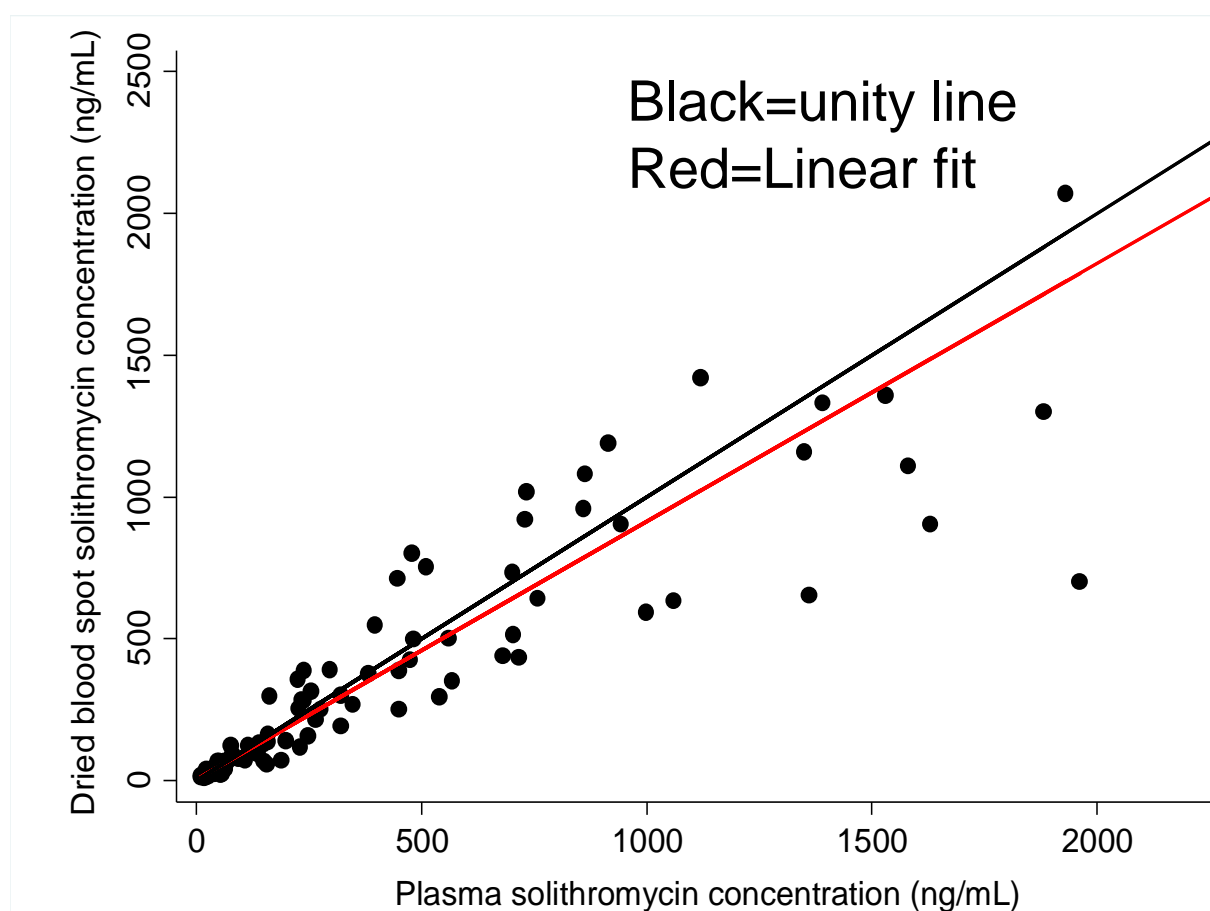
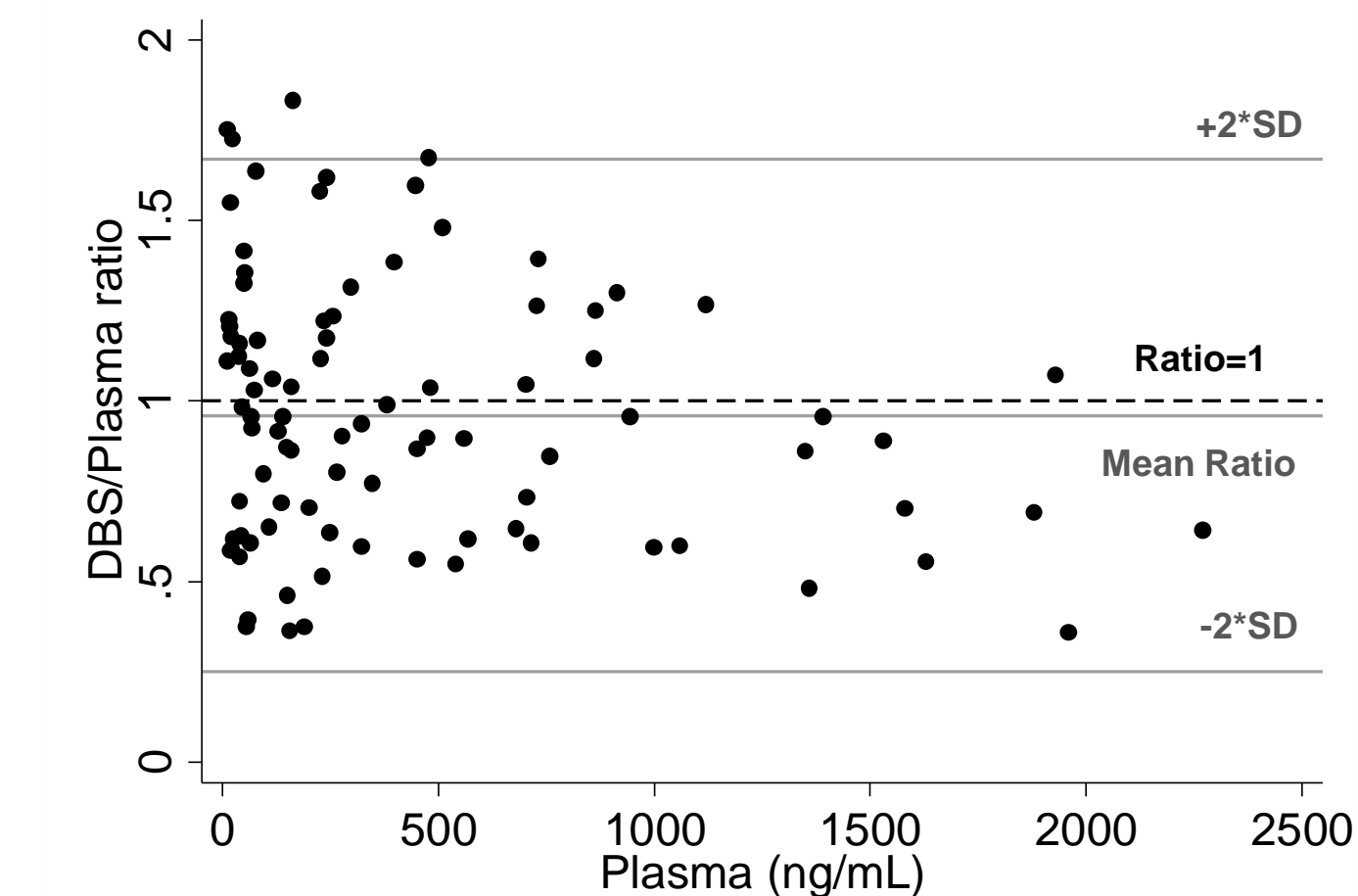


Figure 2. DBS sample vs. plasma solithromycin concentrations.



- 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, \pm 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).

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



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.

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