A Dried Blood Spot Analysis for Solithromycin in Adolescents, Children, and Infants: A Short Communication

Ryan J. Beechinor, PharmD[1], **Michael Cohen-Wolkowiez, MD, PhD**[2,3], **Theresa Jasion, MS**[3], **Christoph P. Hornik, MD, MPH**[2,3], **Jason E. Lang, MD, MPH**[2], **Robert Hernandez, PhD**[4], **Daniel Gonzalez, PharmD, PhD**[1]

[1]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[2]Department of Pediatrics, Duke University Medical Center, Durham, NC, USA

[3]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA

[4]Melinta Therapeutics, Chapel Hill, NC, USA

Abstract

Background: Solithromycin is a fourth-generation macrolide antibiotic with potential efficacy in pediatric community-acquired bacterial pneumonia. Pharmacokinetic (PK) studies of solithromycin in pediatric subjects are limited, therefore application of minimally invasive drug sampling techniques, such as dried blood spots (DBS), may enhance PK study enrollment in children. The objectives of this study were to compare solithromycin concentrations in DBS with those in liquid plasma samples (LPS) and to quantify the effects of modeling DBS concentrations on the results of a population PK model.

Methods: Comparability analysis was performed on matched DBS and LPS solithromycin concentrations collected from two different phase 1 clinical trials of solithromycin treatment in children (clinicaltrials.gov # and #). Comparability of solithromycin concentrations was evaluated based on DBS-LPS ratio, median percentage prediction error (MPPE), and median absolute percentage prediction error (MAPE). The effect of correcting DBS concentrations for both hematocrit and protein binding was investigated. Additionally, a previously published population PK model (NONMEM®) was leveraged to compare parameter estimates resulting from either DBS or LPS concentrations.

Results: A total of 672 paired DBS-LPS concentrations were available from 95 subjects (age: 0–17 years of age. The median (range) LPS and DBS solithromycin concentrations were 0.3 (0.01–12) μg/mL and 0.32 (0.01–14) μg/mL, respectively. MPPE and MAPE of raw DBS to LPS solithromycin concentrations were 5.26% and 22.95%, respectively. Additionally, the majority of

Corresponding Author: Daniel Gonzalez, UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, CB #7569, Chapel Hill, NC 27599-7569, USA. Tel.: +1-919-966-9984; Fax: 919-962-0644; daniel.gonzalez@unc.edu.

Compliance with Ethical Standards: All clinical studies, from which data were obtained, were conducted in accordance with the ethical standards of the institutional and/or national research committee and the Helsinki Declaration.

population PK parameter estimates resulting from modeling DBS concentrations were within 15% of those obtained from modeling LPS concentrations.

Conclusion: Solithromycin concentrations in DBS were similar to those measured in LPS and did not require correction for hematocrit or protein binding.

Keywords

solithromycin; dried blood spots; pharmacokinetics; NONMEM; pediatric drug development; clinical pharmacology

1. INTRODUCTION

The use of dried blood spot (DBS) sampling to quantify drug concentrations is an innovative technique that offers several practical advantages over traditional plasma sampling. These advantages include lower sample volume requirements, simplified collection techniques, and less restrictive storage conditions.[1,2] DBS sampling is particularly useful in neonatal and pediatric populations, in which obtaining liquid plasma samples (LPS) is challenging owing to blood volume restrictions.[3,4] Furthermore, because of both ethical and logistical constraints, robust pharmacokinetic (PK) studies in infants and children are infrequently performed. Therefore, the use of DBS sampling may enable the execution of these PK investigations, which can help improve dosing recommendations in this vulnerable population.[4,5] However, before DBS sampling can be utilized instead of LPS, there are several bioanalytical issues that require assessment, including development of analytical techniques to quantify DBS drug concentrations, characterization of the relationship between DBS and LPS drug concentrations, and evaluation of the impact of hematocrit on DBS drug concentrations.[6,7]

Solithromycin is a novel fourth generation macrolide antibiotic active against common community-acquired bacterial pneumonia (CABP) pathogens, including *Streptococcus pneumoniae, Haemophilus influenzae*, and atypical pathogens.[8,9] In adults, two large phase 3 clinical trials showed that the efficacy of solithromycin was non-inferior to that of moxifloxacin for the treatment of CABP.[10,11] PK data from adult studies have shown that solithromycin has a bioavailability of approximately 67% and a large volume of distribution (V_d) of > 500 L, it is predominantly metabolized by cytochrome P450 3A4, and its pharmacodynamic activity is best characterized by the area under the free drug concentration-time curve/minimum inhibitory concentration (fAUC$_{0-24}$/MIC).[12] Given its potential for the treatment of CABP, the application of DBS sampling to characterize the PK of solithromycin may improve drug dosing recommendations in pediatric patients. Our group previously published both an interim PK analysis of solithromycin LPS and DBS concentrations as well as a population PK model of solithromycin in infants, children, and adolescents.[13,14] In this study, we report the final DBS and LPS analysis for the complete dataset and compare the results of population PK model between the two matrices.

2. MATERIALS AND METHODS

2.1. Patient Data

Data in this study were obtained by combining data from two different phase 1 clinical trials of solithromycin treatment in children/adolescents (CE01-119 and CE01-120; clinicaltrials.gov # and #, respectively). Study CE01-120 included 83 subjects with an age range of 0–17 years of age.[13] Study CE01-119 included 13 adolescents ranging from 12 to 17 years of age.[14] The baseline characteristics of the combined study subjects calculated at the time of first dose were as follows: a median (range) age, 7 years (0–17); total body weight, 23 kg (3.8–105); serum creatinine level, 0.4 mg/dL (0.1–1.2); blood urea nitrogen, 9 mg/dL (2–30); aspartate aminotransferase level, 28 U/L (11–97); alanine aminotransferase level, 23 U/L (5–205); alkaline phosphatase level, 161 IU/L (51–2701); total bilirubin level, 0.3 mg/dL (0.1–10.5); albumin level, 3.6 g/dL (1.5–4.8); and hematocrit value, 34.6% (22.9–47.3). All subjects enrolled in these studies provided informed consents, obtained either from the patient (if of appropriate age according to local requirements), parent, or legally authorized representative. Each enrolling study site had the protocol reviewed and approved by their respective institutional review board.[13,14]

2.2. Drug Administration and PK Sampling

In study CE01-120, solithromycin was administered intravenously (IV) and orally (suspension and capsules) (IV, 6 to 8 mg/kg [400 mg adult maximum]; capsules/suspension, 14 to 16 mg/kg [800 mg adult maximum] on day 1, and 7 to 15 mg/kg [400 mg adult maximum] on days 2 to 5).[13] In study CE01-119, adolescents were administered solithromycin orally (capsules) at doses of 12 mg/kg on day 1 [800 mg adult maximum] and 6 mg/kg daily on days 2 to 5 [400 mg adult maximum].[14] Further details regarding solithromycin dosing are available in published clinical trials.[13,14] Following oral administration, PK samples were collected at 0.5–1.5, 2–4, 8–10, and 23-< 24 h after administration. After IV administration, PK samples were generally obtained within 10 min after completion of a 60-minute infusion, and at 2–4, 8–10, and 23-< 24 h after the start of infusion for the first and multiple doses.[13,14] PK analysis dataset was generated and formatted by Duke Clinical Research Institute by merging clinical database data (dosing, demographics, and laboratory data) with raw concentration values received from the central laboratory. More information on the bioanalysis of solithromycin is available in Supplementary Information 1. All data manipulation and visualization was performed using R (version 3.0.2, R Foundation for Statistical Computing, Vienna, Austria) and RStudio (version 1.0.143, RStudio, Boston, MA, USA) with the packages lattice, latticeExtra, and ggplot2.[15–17]

2.3. Comparability Analyses of DBS-LPS Concentrations

Comparability analyses were performed using a merged dataset, combining solithromycin DBS and LPS concentrations from CE01-119 and CE01-120 trials. Besides the raw concentrations, DBS concentrations were also corrected for hematocrit [(DBS)/(1-(hematrocrit/100))] and protein binding [(DBS)/(1-(hematocrit/100)*(0.3)].[6,18] Bias and imprecision of LPS and DBS concentration comparisons were assessed *via* calculation of

DBS-LPS concentration ratios, median percentage prediction error (MPPE), and median absolute percentage prediction error (MAPE), as follows:

$$DBS:LPS \; ratio \; = \; \left| CONC_{DBS}/CONC_{plasma} \right|$$

$$MPPE \; = \; median \left(100 \; \times \; \left| CONC_{DBS} - CONC_{plasma} \right| / \; CONC_{plasma} \right)$$

$$MAPE \; = \; median \left(100 \; \times \; \left\| CONC_{DBS} - CONC_{plasma} \right\| / \; CONC_{plasma} \right)$$

where, $CONC_{DBS}$ is the concentration of solithromycin in DBS samples and $CONC_{plasma}$ is the concentration of solithromycin in LPS samples. MPPE and MAPE values < 20% were considered acceptable.[19]

2.4. Comparability Analyses of DBS-LPS Population PK Model Results

A previously published population PK model was used to compare parameter estimates obtained from modeling LPS and DBS concentrations.[13] Briefly, this model was developed using 780 solithromycin plasma concentrations from 83 subjects, with age ranging from 4 days to 17 years of age. The final model was a two-compartment model with linear elimination, first-order absorption, an absorption lag time, an allometric scale of clearance (CL), and V_d parameters based on actual body weight. This model also applied a sigmoidal maximum-effect (E_{max}) maturation function to characterize the relationship between postmenstrual age (PMA) and CL.[13]

Population PK model comparability analysis was performed by re-estimating the final model parameter estimates using either LPS or DBS solithromycin concentrations. Modeling analysis was performed using the first-order conditional estimation method in NONMEM® version 7.4 (ICON Development Solutions; Ellicott City, MD, USA). For each matrix, both the final model parameter estimates and the empirical Bayesian estimates (EBEs) were computed and compared. Additionally, MPPE and MAPE values were calculated based on the EBEs of CL and V_d terms as follows:

$$MPPE \; = \; median \left[100 \; \times \; \left(\theta_{DBS} - \theta_{LPS} \right) / \; \theta_{LPS} \right]$$

$$MAPE \; = \; median \left[100 \; \times \; \left\| \left(\theta_{DBS} - \theta_{LPS} \right) \right\| / \; \theta_{LPS} \right]$$

where, θ_{DBS} refers to the PK parameter value derived using DBS solithromycin concentrations and θ_{LPS} refers to the PK parameter value derived using LPS solithromycin concentrations. MPPE and MAPE values < 20% were considered acceptable.[19]

RESULTS AND DISCUSSION

A total of 672 paired DBS-LPS solithromycin samples from 95 subjects were included in this analysis. Correction of DBS solithromycin concentrations for hematocrit and protein binding did not improve the measures of bias and precision; therefore, all further analyses were performed using raw DBS solithromycin concentrations. The median (range) LPS and DBS solithromycin concentrations were 0.3 (0.01–12) μg/mL and 0.32 (0.01–14) μg/mL, respectively. As shown in Figure 1a, an unweighted linear regression ($R^2 = 0.85$) best characterized the correlation between DBS and LPS concentrations. The median (range) DBS to LPS ratio was 1.05 (0.07–18.37). A plot of DBS to LPS ratio *vs.* LPS concentrations is shown in Figure 1b. A log-log plot of DBS *vs.* LPS is shown in Figure 1c. The MPPE and MAPE of raw DBS to LPS solithromycin concentrations were 5.26% and 22.95%, respectively.

The final population PK model parameter estimates resulting from modeling LPS and DBS solithromycin concentrations are shown in Table 1. The vast majority (83.3% [15/18]) of the estimates obtained from modeling DBS solithromycin concentrations were within 15% of those obtained from modeling LPS solithromycin concentrations. The three terms showing > 15% differences between the two matrices were the Hill coefficient for the sigmoidal maturation function (26.3% difference), the maturation half-life as a function of PMA (27.8% difference), and the off diagonal estimate for the covariance between central V_d and peripheral V_d (38.2% difference). Despite these differences, the DBS parameter estimates for CL terms, V_d terms, and the absorption rate constant were all within 10% of their respective LPS parameter estimates. Furthermore, the MPPE and MAPE estimates comparing the EBEs from each matrix for CL, central V_d, and peripheral V_d were –1.71% and 18.9%, 5.48% and 23%, and 6.15% and 18%, respectively.

Consistent with the results from CE01-119 study, solithromycin concentrations in DBS and LPS were comparable, albeit with some variability. This variability might be attributed to multiple factors, including red blood cell partitioning, nonhomogeneous distribution across the blood spot sample, and inherent physicochemical properties of the molecule.[20] A slope of DBS to LPS concentration ratio near unity indicated that significant red blood cell partitioning occurred, which is in agreement with data from a previous study (~75% whole blood:plasma partitioning based on total radioactivity; sponsor data on file). This finding is in line with results obtained for other drugs with high red blood cell partitioning.[21] Besides the comparability of solithromycin DBS and LPS concentrations, population PK modeling results did not differ significantly between the two matrices. Given the similarity in the final model estimates for CL, V_d, and absorption rate constant between the two matrices, it is likely that maintenance dosing recommendations made based on the results of population PK models would not be altered by the use of DBS concentrations.

CONCLUSION

Solithromycin DBS concentrations were similar to LPS concentrations with comparable population PK model results, suggesting that DBS concentrations would result in similar

dosing recommendations if used instead of LPS concentrations. These results support the continued use of DBS sampling techniques in clinical pharmacology research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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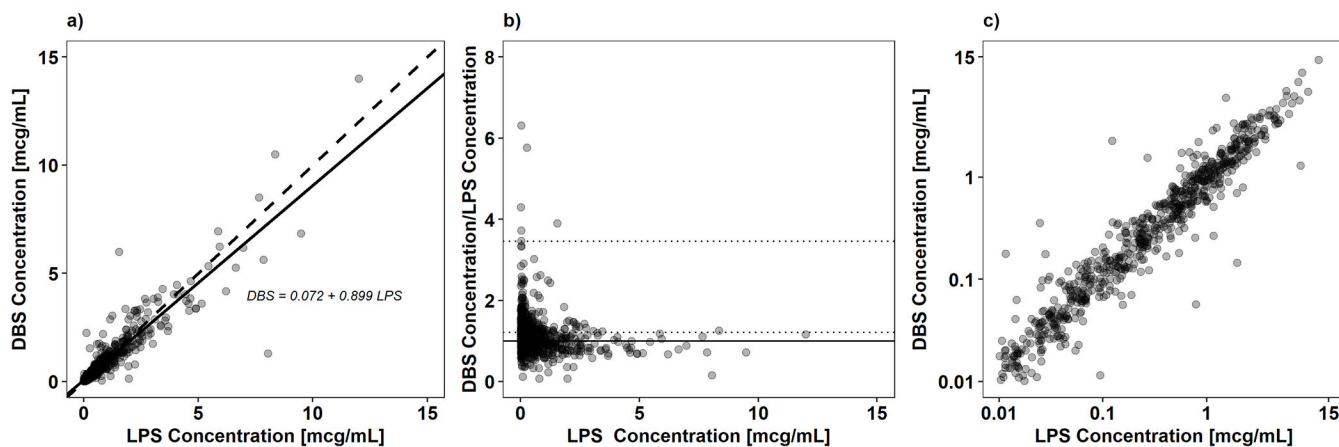
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Figure 1.
Comparability analysis of matched dried blood spot (DBS) and liquid plasma samples (LPS) solithromycin concentrations. Panel a) shows the weighted linear regression of the paired LPS-DBS solithromycin concentrations. The solid and dashed lines represent the unity line and regression fit, respectively. Panel b) shows solithromycin DBS-LPS ratio *versus* LPS solithromycin concentration. The dashed lines denote the mean ratio and $1.96 \times$ standard deviation. The solid black line denotes a ratio of 1. Three ratios > 7 were removed from the figure to allow for improved visualization of the data. Panel c) shows the paired LPS-DBS solithromycin concentrations plotted on a log scale.

Table 1.

Comparison of final population PK model parameter estimates of liquid plasma sample (LPS) concentrations and dried blood spot (DBS) concentrations.

Matrix	LPS Concentrations (780 samples from 95 subjects)		DBS Concentrations (793 samples from 95 subjects)	
Structural Model	**Estimate**	**RSE (%)**	**Estimate**	**RSE (%)**
K_a (h^{-1})	0.381	14	0.353	12
$CL_{POP,70KG}$ (L/h)	55	22	59.5	10
$Vc_{POP,70KG}$ (L)	162	16	171	15
$Q_{POP,70KG}$ (L/h)	23.4	30	23	29
$Vp_{POP,70KG}$ (L)	119	12	123	12
F capsule (%)	69.1	18	70.2	21
F suspension (%)	52.9	19	55	14
LAG capsule (h)	0.494	2	0.491	3
LAG suspension (h)	0.365	24	0.325	20
HILL	1.09	77	0.81	17
TM_{50} (weeks)	52.6	40	67.2	30
Inter-individual Variability (IIV)				
IIV CL (%)	81.9	8	79.4	2
Covariance CL-Vc	0.569	25	0.585	22
IIV Vc (%)	89.6	13	93.1	20
Covariance Vc-Vp	0.262	38	0.362	31
IIV Vp (%)	53.7	28	47	51
Covariance CL-Vp	0.355	38	0.376	30
Residual Variability				
Proportional error (%)	53.9	9	55.5	9

K_a, absorption rate constant; $CL_{POP,70KG}$, population clearance estimate scaled to a 70-kg adult; $Vc_{POP,70KG}$, population central volume of distribution estimate scaled to a 70-kg adult; $Q_{POP,70KG}$, population inter-compartmental clearance estimate scaled to a 70-kg adult; $Vp_{POP,70KG}$, population peripheral volume of distribution estimate scaled to a 70-kg adult; F, bioavailability; LAG, lag time (h) in drug absorption; HILL, Hill coefficient for the sigmoidal maturation function; TM_{50}, maturation half-life calculated as a function of post-menstrual age (weeks); IIV CL, inter-individual variability in drug clearance reported as CV%; Covariance CL-Vc, covariance between CL and Vc; IIV Vc, inter-individual variability in central volume of distribution reported as CV%, Covariance Vc-Vp, covariance between CL and Vc; IIV Vp, inter-individual variability in peripheral volume of distribution reported as CV%; and Covariance CL-Vp, covariance between CL and Vp. Proportional error reported as CV%