Solithromycin Pharmacokinetics in Plasma and Dried Blood Spots and Safety in Adolescents

Daniel Gonzalez, Debra L. Palazzi, Leena Bhattacharya-Mithal, Amira Al-Uzri, Laura P. James, John Bradley, Natalie Neu, Theresa Jasion, Christophe P. Hormik, P. Brian Smith, Daniel K. Benjamins, Jr, Prabhavathi Fernandes, Michael Cohen-Wolkowiez

Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina, USA; Infectious Diseases Section, Baylor College of Medicine, Houston, Texas, USA; Ann and Robert H. Lurie Children’s Hospital of Chicago, Chicago, Illinois, USA; Oregon Health & Science University, Portland, Oregon, USA; Arkansas Children’s Hospital Research Institute, Little Rock, Arkansas, USA; University of California San Diego Medical Center, San Diego, California, USA; Columbia University Medical Center, New York, New York, USA; Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina, USA; Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina, USA; Cempra, Inc., Chapel Hill, North Carolina, USA.

We assessed the pharmacokinetics and safety of solithromycin, a fluoroketolide antibiotic, in a phase 1, open-label, multicenter study of 13 adolescents with suspected or confirmed bacterial infections. On days 3 to 5, the mean (standard deviation) maximum plasma concentration and area under the concentration versus time curve from 0 to 24 h were 0.74 μg/ml (0.61 μg/ml) and 9.28 μg · h/ml (6.30 μg · h/ml), respectively. The exposure and safety in this small cohort of adolescents were comparable to those for adults. (This study has been registered at ClinicalTrials.gov under registration no. NCT01966055.)

Invasive infections due to drug-resistant bacteria are increasingly common and often fatal. In the United States, approximately 2 million people have drug-resistant infections, resulting in 23,000 deaths annually (1). Solithromycin is a new fluoroketolide antibiotic with activity against a wide array of bacteria causing respiratory tract infections and other pathogens. Solithromycin is under investigation for oral and intravenous use in children. We performed a phase 1, open-label, multicenter pharmacokinetics (PK) and safety study of oral solithromycin in adolescents.

We enrolled male and female adolescents, aged 12 to 17 years (inclusive), with suspected or confirmed bacterial infections (ClinicalTrials.gov registration number NCT01966055). Adolescents were enrolled and administered solithromycin (capsules) as an add-on therapy (12 mg/kg of body weight on day 1 [800-mg adult maximum] and 6 mg/kg daily on days 2 to 5 [400-mg adult maximum]) for up to 5 days. Solithromycin was taken without regard to food. Written informed consent was obtained from the parent or other legally authorized representative and informed assent from the patient (if age appropriate according to local requirements). All study sites had the protocol reviewed and approved by their institutional review boards. The first adolescent was enrolled on 17 February 2014, and the last adolescent completed the study on 5 September 2014. An independent data monitoring committee (DMC) assessed the overall study status and safety of patients. The DMC met prior to the first patient enrollment, after the first four subjects had completed enrollment, and after the study completion to review the trial data.

Paired plasma and dried blood spot (DBS) PK samples were collected at 0.5 to 1.5, 2 to 4, 8 to 10, and 23 to 24 h after the first and multidose administrations of solithromycin. Samples for both matrices were analyzed for solithromycin by a central laboratory (MicroConstants, San Diego, CA, USA) using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods for both matrices. The accuracy and precision were within the Food and Drug Administration bioanalytical assay validation criteria for both methods (e.g., ±15 to 20%). The solithromycin lower limit of quantitation was 0.01 μg/ml, and the calibration range was 0.01 to 20 μg/ml for both matrices.

A noncompartmental PK analysis was performed with Phoenix WinNonlin (version 6.3; Certara, St. Louis, MO, USA) using solithromycin plasma concentration versus time data. Following the first dose and on days 3 to 5, the maximum concentration ($C_{\text{max}}$) and the area under the concentration versus time curve from 0 to 24 h (AUC$_{0-24}$) were determined. The AUC$_{0-24}$ was calculated using the trapezoidal method. The solithromycin concentrations in traditional plasma and DBS samples were compared using weighted linear regression, and the overall presence of bias and imprecision was assessed through the calculation of the median percentage prediction error (MPPE) and the median absolute percentage prediction error (MAPE) (2). MPPE and MAPE values of <15% were considered acceptable (3, 4). Also, we repeated the analyses after correcting the DBS concentrations for hematocrit (3).

Thirteen adolescents were enrolled, and all completed the clinical trial. The demographic and clinical laboratory variables are summarized in Table 1. The most frequently reported primary medical conditions were cystic fibrosis (3 [23%]), skin infection (3...
One adolescent (8%) received oxcarbazepine, and another adolescent received nafcillin throughout solithromycin treatment.

On day 1, 8 of the 13 adolescents (62%) received an 800-mg loading dose (adult maximum). The median (range) loading dose was 800 mg (400 to 800 mg) or 12.3 mg/kg (9.5 to 13.3 mg/kg). Thereafter, all adolescents received a 400-mg daily maintenance dose except for two patients, who received 200-mg or 300-mg daily doses. The median (range) maintenance dose was 400 mg (200 to 400 mg) or 6.3 mg/kg (4.8 to 6.8 mg/kg). Treatment duration was 3, 4, and 5 days for 46% (6/13), 23% (3/13), and 31% (4/13) of the adolescents, respectively. A total of 118 plasma and 117 DBS samples were collected, of which 96 and 95 samples (both 81%), respectively, had quantifiable solithromycin concentrations; 16 (73%) of the 22 samples with concentrations below the quantification limit were collected from three adolescents. Solithromycin concentration versus time curves are shown in Fig. 1.

Overall, the $C_{\text{max}}$ and $AUC_{0–24}$ values for solithromycin were within the range of the observed values (mean [standard deviation]) in healthy adult subjects (Table 2). Four adolescents in this study had lower than expected day 3 to 5 solithromycin plasma exposures. Two of these adolescents had cystic fibrosis, and one adolescent (without cystic fibrosis) received blood transfusions on the day of the PK sampling. One adolescent had therapeutic exposures following a loading dose, but low exposures after multiple dosing (for both the parent drug and metabolites); a review of this adolescent’s medical history and concomitant medications did not provide insight into the cause of this observation.

A total of 92 matched pairs of plasma and DBS sample solithromycin concentrations from 12 adolescents were included in the comparability analysis. The median (range) hematocrit was 38% (22 to 45%). Weighted linear regression showed a linear relationship between the DBS and plasma sample solithromycin concentrations (slope 0.91 [95% confidence interval, 0.82 to 0.99]) (Fig. 2). Similar results were observed using nonparametric regression. The MPPE for the comparison of

### Table 1: Adolescent characteristics and study dosing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td></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>Dose (mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>12.3 (9.5–13.3)</td>
</tr>
<tr>
<td>Days 2–5</td>
<td>6.3 (4.8–6.8)</td>
</tr>
<tr>
<td>Age (yr)</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 gender</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Non-Hispanic or Latino</td>
<td>10 (77)</td>
</tr>
</tbody>
</table>

$^a$ Values are median (range) or no. (%).

### Table 2: Solithromycin exposure in adolescents and historically healthy adult subjects$^b$

<table>
<thead>
<tr>
<th>Day(s)</th>
<th>Parameter</th>
<th>Adolescents ($n = 13$$^b$)</th>
<th>Healthy adults ($n = 5/10$$^c$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>0.97 (0.73)</td>
<td>1.32 (0.92)</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0–24}$ (µg · h/ml)</td>
<td>11.62 (8.55)</td>
<td>13.67 (9.56)</td>
</tr>
<tr>
<td>3–5</td>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>0.74 (0.61)</td>
<td>1.09 (0.52)</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0–24}$ (µg · h/ml)</td>
<td>9.28 (6.30)</td>
<td>13.27 (7.36)</td>
</tr>
</tbody>
</table>

$^b$ Data are means (SD).

$^c$ For the maximum concentration ($C_{\text{max}}$), all subjects contributed data. For the area under the concentration versus time curve from 0 to 24 h ($AUC_{0–24}$), 12 and 10 adolescents contributed data on day 1 and days 3 to 5, respectively.

$^d$ Day 1 adult estimates were obtained from healthy subjects that received an 800-mg single dose ($n = 5$) (5). The area under the concentration versus time curve ($AUC$) estimate reported represents AUC from time zero to the last sample time point. The day 3 to 5 adult estimate used for comparison represents observed exposure on day 7 in healthy adults receiving 400 mg/day ($n = 10$) (5).

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**FIG 1** Solithromycin plasma concentration versus time after dose in adolescents. Each line denotes an individual subject concentration versus time curve.
the DBS to plasma sample solithromycin concentrations was 
−6.9%, and the MAPE was 29.0%; the latter is outside our
predefined acceptable cutoff. Correcting for hematocrit did not
provide any additional improvement in the agreement between
plasma and DBS sample concentrations.

Twelve adverse events were reported in eight adolescents;
nine (75%) of these events were unrelated to solithromycin
(Table 3). Two separate episodes of mild headache and one
episode of increased hepatic transaminases (<3× upper limit
of normal) seemed to be related to the study drug in three
subjects. All three drug-related adverse events subsided upon
discontinuation of solithromycin. The adolescent with in-
creased hepatic transaminases had a medical history of cystic
fibrosis and pancreatic insufficiency and received concomitant
medications that might potentially alter hepatic transaminases
(i.e., azithromycin and cefepime).

In this study, due to impending hospital discharge,
~50% of the adolescents in our study had multiple-dose PK Assessments
on day 3, which limited the ability to compare these data to
adult solithromycin exposures collected in healthy volunteers
after at least 5 days of dosing. Despite the early PK sampling
(day 3 of therapy), on average, the solithromycin exposures in
the adolescents with quantifiable PK data after multiple doses
were within the range of exposures observed in these healthy
adult volunteers. In adults, exposures in the epithelial lining
fluid were approximately 10-fold higher (6), and similar pen-
etration may be seen in adolescents although this was not di-
rectly measured. Therefore, these data support the use of a
12-mg/kg loading dose (up to 800 mg) and 6-mg/kg mainte-
nance doses (up to 400 mg) in future safety studies of solithro-
mycin in adolescents.

Notably, the range of solithromycin exposures on day 1 and
days 3 to 5 varied substantially between adolescents. This effect is
likely multifactorial and might be related to the inherent intersub-
ject variability in drug concentrations characteristic of macrolides
(7–9), underlying disease (e.g., cystic fibrosis) (10), concomitant
medications (e.g., CYP3A4 inducers and pH modifiers), limita-
tions of our sparse sampling approach, and/or timing of PK sam-
ping (e.g., sampling on day 3 versus day 5). In the three patients
with cystic fibrosis, there was a trend toward lower solithromycin
exposure with multiple dosing compared with that in patients
without cystic fibrosis and with adult values. This finding may be
due to the drug absorption limitations of cystic fibrosis (10, 11).
Nonetheless, the current sample size limits our ability to make
robust conclusions with regard to the comparison between cystic
fibrosis and non-cystic fibrosis patients. Another potential con-
founding variable may have been the concomitant exposure to
oxcarbazepine and nafcillin, which are CYP3A4-inducing drugs,
in two adolescents. Although clinical data available to evaluate the
effect of nafcillin on the PK of CYP3A4 substrates are limited, in vitro
data suggest that nafcillin may induce the protein expres-
sion of CYP3A4 (12).

The solithromycin concentrations in DBS and plasma samples
were comparable, albeit with substantial variability, particularly at
the low end of the concentration range (see Fig. S1 in the supple-
mental material). This variability may have resulted from variabil-
ity in red blood cell partitioning, nonhomogeneous distribution
across the blood spot sample, inherent physicochemical proper-
ties of the molecule, or sample hematocrit (13). However, ac-
counting for sample hematocrit in our study did not improve
agreement between the two matrices. A slope near unity of the
DBS to plasma concentration ratio indicates that significant red
blood cell partitioning occurs, which is in agreement with previ-
ously observed data (~75% whole blood/plasma partitioning
based on total radioactivity; sponsor data [Cempra, Inc., Chapel
Hill, NC] on file) (14).

We found solithromycin to be well tolerated in a small sample
of adolescents. Although we concluded that these three adverse
events were related to the study drug, these adolescents were re-
ceiving a variety of concomitant medications, which might also
account for the adverse events. The favorable safety profile of so-
 lithromycin is consistent with that in phase 1 and 2 adult studies,
where reports of headache were mild, and mean changes in labo-
atory parameters were not deemed clinically significant. A he-
patic impairment study found no difference in safety relative to
healthy adults (15) and reported that no dosage adjustment is
needed in patients with mild, moderate, or severe disease. A future
phase 2/3 study will be performed to assess the safety of solithro-
TABLE 3 Reported adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. (%) in all patients (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no.</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>Serious</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Headache (mild severity)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Increased transaminases (&lt;3× ULN*)</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
</tr>
<tr>
<td>FU</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>0</td>
</tr>
<tr>
<td>Headache (mild severity)</td>
<td>0</td>
</tr>
<tr>
<td>Increased transaminases (&lt;3× ULN*)</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
</tr>
</tbody>
</table>

*ULN, upper limit of normal.
mycin in children with community-acquired bacterial pneumonia (CABP).

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D. Gonzalez and M. Cohen-Wolkowiez wrote the manuscript; D. Gonzalez, C. P. Hornik, and M. Cohen-Wolkowiez analyzed the data; D. Gonzalez, P. B. Smith, D. K. Benjamin, Jr., P. Fernandes, and M. Cohen-Wolkowiez designed the research; D. Gonzalez, D. L. Palazzi, L. Bhattacharya-Mithal, A. Al-Uzri, L. P. James, J. Bradley, N. Neu, T. Jasion, C. P. Hornik, P. B. Smith, D. K. Benjamin, Jr., K. Keedy, P. Fernandes, and M. Cohen-Wolkowiez performed the research.

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