Rifapentine Pharmacokinetics and Tolerability in Children and Adults Treated Once Weekly With Rifapentine and Isoniazid for Latent Tuberculosis Infection

Marc Weiner,1,2,a Radojka M. Savic,3,a William R. MacKenzie,4 Diane Wing,1 Charles A. Peloquin,5 Melissa Engle,1 Erin Bliven,1 Thomas J. Prihoda,6 Jonathan A. L. Gelfond,7 Nigel A. Scott,4 Susan M. Abdel-Rahman,8 Gregory L. Kearns,8 William J. Burman,9 Timothy R. Sterling,10 and M. Elsa Villarino4; for the Tuberculosis Trials Consortium PREVENT TB Pharmacokinetic Group

1Department of Medicine, University of Texas Health Science Center, San Antonio; 2Veterans Administration Medical Center, San Antonio, Texas; 3University of California at San Francisco, School of Pharmacy, Bioengineering and Therapeutic Sciences; 4Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia; 5University of Florida, College of Pharmacy, Gainesville; 6Department of Pathology, University of Texas Health Science Center, San Antonio; 7Department of Epidemiology and Biostatistics, University of Texas Health Science Center, San Antonio; 8Pediatrics, Children’s Mercy Hospitals and Clinics, Kansas City, Missouri; 9Denver Health, Denver Public Health, Colorado; and 10Vanderbilt Universities, Medicine, Nashville, Tennessee

Corresponding Author: Marc Weiner, MD, VAMC, Division Infectious Diseases (111), 7400 Merton Minter Blvd, San Antonio, TX 78229-4404. E-mail: weiner@uthscsa.edu.

Presented in part: 5th International Workshop on Clinical Pharmacology of Tuberculosis Drugs, San Francisco, CA.

aM. W. and R. M. S. contributed equally to this work.

Background. In a phase 3, randomized clinical trial (PREVENT TB) of 8053 people with latent tuberculosis infection, 12 once-weekly doses of rifapentine and isoniazid had good efficacy and tolerability. Children received higher rifapentine milligram per kilogram doses than adults. In the present pharmacokinetic study (a component of the PREVENT TB trial), rifapentine exposure was compared between children and adults.

Methods. Rifapentine doses in children ranged from 300 to 900 mg, and adults received 900 mg. Children who could not swallow tablets received crushed tablets. Sparse pharmacokinetic sampling was performed with 1 rifapentine concentration at 24 hours after drug administration (C24). Rifapentine area under concentration-time curve (AUC) was estimated from a nonlinear, mixed effects regression model (NLME).

Results. There were 80 children (age: median, 4.5 years; range, 2–11 years) and 77 adults (age: median, 40 years; all ≥18 years) in the study. The geometric mean rifapentine milligram per kilogram dose was greater in children than in adults (children, 23 mg/kg; adults, 11 mg/kg). Rifapentine geometric mean AUC and C24 were 1.3-fold greater in children (all children combined) than in adults. Children who swallowed whole tablets had 1.3-fold higher geometric mean AUC than children who received crushed tablets, and children who swallowed whole tablets had a 1.6-fold higher geometric mean AUC than adults. The higher rifapentine doses in children were well tolerated. To obtain rifapentine exposures comparable in children to adults, dosing algorithms modeled by NLME were developed.

Conclusions. A 2-fold greater rifapentine dose for all children resulted in a 1.3-fold higher AUC compared to adults administered a standard dose. Use of higher weight-adjusted rifapentine doses for young children are warranted to achieve systemic exposures that are associated with successful treatment of latent tuberculosis infection in adults.

Key words. children; pharmacokinetics; rifapentine; treatment; tuberculosis.
INTRODUCTION

The World Health Organization has estimated that one-third of the world’s population is infected with latent tuberculosis infection (LTBI); 1 million children are diagnosed annually with active tuberculosis (TB) [1]; and in high-burden countries, children represent 20% to 40% of TB cases [2, 3]. Based on clinical trials, the United States Centers for Disease Control and Prevention recommended a new short-course alternative treatment for LTBI in otherwise healthy people, 12 years of age and older, at high risk for developing active TB [4–6].

In the PREVENT TB phase 3, randomized treatment trial of 8053 patients with LTBI, a 12-dose, once-weekly rifapentine and isoniazid regimen (3HP) had similar efficacy and tolerability as a 9-month course of daily isoniazid [4]. A previous single-dose pharmacokinetic study in children aged 2 to 11 years showed low rifapentine area under the concentration-time curve (AUC), dose-normalized AUC, and peak concentration compared with historical data in adults who received comparable milligram per kilogram doses [7, 8]. Therefore, in the PREVENT TB trial, reported rifapentine doses (milligram per kilogram) were higher for young children than adults. In adolescents (age, 12–15 years), reported rifapentine pharmacokinetic parameters were similar to those in adults [6, 8–10].

The purpose of the present study, which was a pharmacokinetic component of the PREVENT TB trial, was (1) to determine the rifapentine AUC in children who were given the higher rifapentine (milligram per kilogram) doses and (2) to compare the rifapentine AUC between children and adults.

MATERIALS AND METHODS

Experimental Design

Children and adults were recruited to the present study as a convenience sample from the PREVENT TB trial. All patients in the treatment trial had LTBI (positive tuberculin skin test) and no evidence of TB. Risk groups in the treatment trial were recent close contacts of patients with pulmonary TB, patients infected with human immunodeficiency virus, patients with a recent tuberculin skin test conversion, or patients with fibrotic or fibronodular abnormalities consistent with old, healed TB on chest radiograph. Children enrolled in this study were aged 2–11 years, and children and adults were treated with 3HP.

The objective of the PREVENT TB treatment trial was to attain comparable rifapentine exposures between children and adults by administering higher weight-adjusted milligram per kilogram doses to children than adults. The objective of the pharmacokinetic component study of the PREVENT TB trial was to characterize the rifapentine exposures achieved in the convenience sample of children using the PREVENT TB dosing schedule. Rifapentine was given as 150-mg tablets (Priftin, sanofi-aventis, Italy). For the PREVENT TB trial and the present study, the once-weekly rifapentine doses in children were based on body weight (range, 300–900 mg) (Table 1), and the rifapentine dose in adults was 900 mg (except for 1 person who had a body weight <45 kg and received 750 mg of rifapentine). The dosing algorithm was based on simulations that used the relation between age and dose-corrected total body exposure in children and adults [7, 8]. Children who could not swallow tablets were administered the same doses (Table 1) of crushed rifapentine and isoniazid tablets as a suspension in soft food or liquid. Food that was consumed 2 hours before and 1 hour after drug administration was documented. The once-weekly dose of isoniazid was 25 mg/kg for children (maximum, 900 mg) and 15 mg/kg for adults (maximum, 900 mg). Adverse events during treatment and follow-up were documented (Supplemental material, Methods). The Institutional Review Boards of the Centers for Disease Control and Prevention and of participating study sites approved the study. Informed consent was obtained from adult participants or guardians, and assent was given by children aged ≥7 years.

Rifapentine and Metabolite Levels

A single plasma sample was collected to determine rifapentine and metabolite (25-desacetyl-rifapentine) concentration at 24 hours after administration of study drugs (C24). In 3 independent rifapentine pharmacokinetic studies that used intensive sampling [7–8, 10], there was a high correlation between rifapentine C24 and AUC (Supplemental Table S1). After ≥3 once-weekly treatment doses as part of the PREVENT TB trial, rifapentine and isoniazid were given by direct observation of a study team member. A 2-ml venous blood sample for pharmacokinetic analysis was obtained 23–25 hours after drug administration and was processed as previously described [8, 11]. Plasma concentrations of rifapentine and metabolite (25-desacetyl-rifapentine) were determined with a validated high pressure liquid chromatography assay (Supplemental Table S1).

Table 1. Rifapentine Dosing for Children With Latent Tuberculosis Infection in the Present Studya

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Rifapentine Dose (mg)</th>
<th>Rifapentine Dose (mg/kg)</th>
<th>Age of Study Patients, y (mean ± standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–14</td>
<td>300</td>
<td>21–30</td>
<td>2.6 ± 0.8</td>
</tr>
<tr>
<td>&gt;14–25</td>
<td>450</td>
<td>18–32</td>
<td>4.3 ± 1.6</td>
</tr>
<tr>
<td>&gt;25–32</td>
<td>600</td>
<td>19–24</td>
<td>7.4 ± 2.2</td>
</tr>
<tr>
<td>&gt;32–50</td>
<td>750</td>
<td>15–23</td>
<td>9.7 ± 2.4</td>
</tr>
<tr>
<td>&gt;50</td>
<td>900</td>
<td>≤18</td>
<td>38.8 ± 12.9</td>
</tr>
</tbody>
</table>

aN = 80 children. Same dosing guideline was used for children in the PREVENT TB trial.
For the rifapentine analyses of the PREVENT TB samples, within-sample precision was 3.61% and validation precision across all rifapentine standards were 3.49%–10.65%.

**Population Pharmacokinetic Model**

Rifapentine AUC from 0 to time infinity (AUC_{0-inf}) was estimated from a nonlinear, mixed effects regression model (NLME) (NONMEM, version 7 software). The model was developed with historical pharmacokinetic data from 35 pediatric subjects without TB who had intensive sampling after a single dose of rifapentine [7, 9]; 35 adult patients with TB in continuation phase therapy who received once-weekly rifapentine and isoniazid and who underwent intensive sampling [8]; and 157 patients with a single C24 sample in the PREVENT TB study who received ≥ 3 once-weekly doses of rifapentine and isoniazid [10]. The model used 1634 rifapentine and metabolite (25-desacetyl-rifapentine) concentration levels from 227 children and adults. Concentration values below the lower limit of quantification were excluded from the pharmacokinetic evaluation. For both children and adults, a model for rifapentine was developed, metabolite data were added, and the rifapentine and metabolite data were analyzed simultaneously. After separate models were established for children and adults, the 2 models were combined (Figure 1). The basic model structure was a 1-compartment disposition model. The individual parameters were assumed log-normally distributed and residual variability was described with combined error model. The model building process (Figure 2) was guided by the likelihood ratio test, diagnostic plots, and internal model validation techniques, including visual and numerical predictive checks. The transit compartment chain model was superior compared with other models tested (compared to first-order absorption, the improvement in GOF was significant \( P < 10^{-30} \)). The final model was scaled allometrically. It was parameterized using oral clearance (CL/F), oral volume of distribution (V/F), clearance of metabolite corrected for the fraction of metabolized drug (Clm/Fm), and volume of the metabolite corrected for the fraction of metabolized drug (Vm/Fm) and included covariates of subject weight, age, rifapentine dose (milligram), tablet integrity (crushed or whole tablet), and food ingestion with study drug (Supplemental material, Methods). The final model was represented by equations 1–3 (Table 2), and the estimation of model pharmacokinetic parameters and the relation between covariates and parameters were represented by equations 1–9 (Table 2).

---

Figure 1. Modeling strategy for rifapentine and metabolite in children and adults treated for latent tuberculosis infection in the PREVENT TB trial. A detailed description of the pharmacokinetic modeling methodology is located in the Supplemental material (Methods). Abbreviations: PK, pharmacokinetic; TB, tuberculosis.
Data analyses were performed with statistical software (NCSS 2007, NCSS, Kaysville, UT; and SAS for Windows, version 9.3, SAS Institute Inc., Cary, NC). Differences between groups were determined using the t test (after one-way analysis of variance [ANOVA]) for continuous variables and \( \chi^2 \) test for categorical data. The 2 subgroups of children were compared to adults with a contrast t test and one-way ANOVA. Area under concentration-time curve and C24 were reported as geometric mean (90% confidence interval), ratio of the geometric mean and median (5th and 95th percentiles, respectively). Data were transformed to the natural logarithm to determine (1) whether variances were more homogeneous with the logarithmic than linear scale and (2) whether the logarithmic distribution better approximated a normal distribution. The natural logarithm results were transformed back to the original scale to report mean values. Statistically significant difference was defined by \( P < .05 \).

RESULTS

Study Population

Of 109 children enrolled in PREVENT TB treatment trial after the pharmacokinetic study was open at participating study sites, a convenience sample of 81 (74%) children were enrolled in this study. Of the 81 children enrolled, 1 child was excluded from the analysis because a pharmacokinetic sample could not be drawn, leaving 80 children in the study. Most children were aged <8 years (Table 3). In the 80 adults enrolled in this study, 3 adults were excluded because the pharmacokinetic sample could not be drawn or insufficient sample volume was obtained (2 adults), leaving 77 adults in the study. Most patients were white and Hispanic (Table 4). Most children took crushed tablets, and these children were significantly younger than children who took whole tablets (Table 4). All adults took whole tablets, and most children and adults took drugs with food (Table 4). The geometric mean dose of rifapentine per kilogram body weight was greater in children (23 mg/kg; range, 12–32 mg/kg) than adults (11 mg/kg; range, 5–17 mg/kg; \( P < .01 \)) (Table 5).

Rifapentine Pharmacokinetics

The rifapentine geometric mean AUC0-inf and C24 were respectively 31% and 28% greater in children than adults (Table 5; Figure 3). In children, the rifapentine geometric mean AUC0-inf was significantly greater with whole versus crushed tablets, and AUC0-inf was significantly greater in children with whole rifapentine tablets than in adults (Table 5; Figures 3 and 4). Eight of 10 children who took drug without food and 65 (93%) of 70 children who took drug with food had rifapentine AUC0-inf >80% of the geometric mean rifapentine AUC0-inf of all adults in the present study. The geometric mean AUC0-inf of the metabolite (25-desacetyl-rifapentine) was similar to that of rifapentine in both children and adults (Table 5; Figure 4).

Apparent oral clearance per kilogram of body weight was significantly higher in children than in adults: clearance for the youngest child (age, 2 years; body weight, 12 kg) was 0.052 L/h × 1/kg, decreasing to the fully matured value of 0.026 L/h × 1/kg (adult clearance). A maturation function was developed because clearance in very young children was higher than that anticipated from only size difference, and accounted for by allometric scaling. Clearance maturation that was expected from growth (weight gain) and estimated in the model showed an increase in clearance in children that was dependent on age (Figure 5). The estimated increase in clearance per kilogram body weight, which was potentially caused by increased metabolic activity, was 22% for the youngest child (age, 2 years). This effect was revealed in a plot showing rifapentine clearance and age after incorporation of allometric scaling. It was confirmed by the decreased ratio of clearance of rifapentine to clearance of metabolite in very young children compared to adults, suggesting higher metabolic activity in very young children.

Children who could not swallow the whole tablet and received the formulation crushed had a decrease in relative bioavailability (26%) compared to the bioavailability of the whole tablet. There was no autoinduction with once-weekly dosing. Food increased bioavailability by 40%. The relative bioavailability in adults was estimated at 0.96 for the 900-mg dose and 0.76 for the 1200-mg dose. In addition to significantly higher clearance in children than in
Table 2. Pharmacokinetic Model for Rifapentine and Metabolite (25-Desacetyl-rifapentine) in Children and Adults With Latent Tuberculosis Infection

<table>
<thead>
<tr>
<th>Equation No.</th>
<th>Description</th>
<th>Equation</th>
</tr>
</thead>
</table>
| 1            | Rifapentine absorption kinetics | \[
\frac{dA_1}{dt} = \frac{F \times \text{Dose} \times k_{\text{a}} \times (k_{\text{tr}} \times t)^n \times e^{-k_{\text{tr}} \times t}}{n!} - k_{\text{tr}} \times A_1
\] |
| 2            | Rifapentine disposition kinetics | \[
\frac{dA_2}{dt} = k_{\text{a}} \times A_1 - \frac{CL}{V} \times A_2
\] |
| 3            | 25-Desacetyl-rifapentine disposition kinetics | \[
\frac{dA_3}{dt} = \frac{CL}{V} \times A_2 - \frac{CLM}{VM} \times A_3
\] |
| 4            | Rifapentine CL and its relationship with age and weight | \[
CL = TVCL \times \left(1 - \frac{\text{Effsize} + \text{Effsize} \times e^{-(\text{Age} - 2) \times \frac{\ln(2)}{\text{MatHL}}}}{\left(\frac{WT}{WT_{\text{median}}}\right)^{0.75}}\right) \times \left(\frac{WT}{WT_{\text{median}}}\right)^{0.75}
\] |
| 5            | 25-Desacetyl-rifapentine clearance | \[
CLm = TVCLm \times \left(\frac{WT}{WT_{\text{median}}}\right)^{0.75}
\] |
| 6            | Rifapentine central volume | \[
V_c = TVVc \times \left(\frac{WT}{WT_{\text{median}}}\right)^{1}
\] |
| 7            | 25-Desacetyl-rifapentine central volume | \[
V_m = TVVm \times \left(\frac{WT}{WT_{\text{median}}}\right)^{1}
\] |
| 8            | Bioavailability expression and its relationship to dose, crushing, and food | if tablet = crushed, \(F = 1 + \theta_{\text{crushed}}\), \(\theta_{\text{crushed}} = \text{decrease in F by crushing the tablet}\) if Dose = 900 mg, \(F = \theta_{900\text{mg}} = \text{Relative bioavailability for 900 mg dose}\) if Dose = 1200 mg, \(F = \theta_{1200\text{mg}} = \text{Relative bioavailability for 1200 mg dose}\) |
| 9            | Rifapentine transit rate constant | \[
k_{tr} = \frac{n+1}{MTT}
\] |

Abbreviations: A1, amount of rifapentine in the absorption compartment; A2, amount of rifapentine in plasma; A3, amount of 25-desacetyl-rifapentine in plasma; CL, rifapentine oral clearance; CLm, clearance of 25-desacetyl-rifapentine; Effsize, maximal increase in CL/kg observed at age of 2 years; F, bioavailability; Dose, drug dose; ka, absorption rate constant; ktr, transit rate constant between 2 neighboring absorption transit compartments; MatHL, maturation half life; MTT, mean transit time to reach absorption compartment; n, total number of transit compartments; t, time; TV, typical value of pharmacokinetic parameters for 70 kg subject; V, rifapentine volume of distribution; Vm, volume of distribution of 25-desacetyl-rifapentine; WT, weight.
adults, children had a more delayed absorption rate than adults, which was evidenced by the longer mean transit time (children, 0.61 h; adults, 0.03 h; \( P < .001 \)). The between-subject variability in clearance was 40%. The full variance-covariance matrix was estimated for rifapentine clearance that was corrected for bioavailability (CL/F), metabolite clearance (CLm) that was corrected for fraction metabolized (Fm; CLm/Fm), and rifapentine volume of distribution that was corrected for bioavailability (V/F), indicating a high correlation among these 3 parameters (Table 6). A visual predictive check for both rifapentine and metabolite showed good agreement between the observed and model predicted data for all age groups (Figure 6).

To obtain rifapentine exposures estimated to be comparable in children and adults, dosing algorithms modeled by NLME were developed. Percentile weights were initially identified in the algorithm with the covariates of children's age and weight (Table 7A). Modeled rifapentine doses were then estimated for use with whole tablets (Table 7B).
or crushed tablets (Table 7C) with children’s age and percentile weight.

Safety and Tolerability of Children and Adults in the Pharmacokinetic Study

The rifapentine and isoniazid regimen were well tolerated by most children. In the present study, 10 patients (3 children, 7 adults) reported a total 11 adverse events during the 12-dose treatment study, and no serious adverse event was reported (Table 8). There were 3 patients in the present study who discontinued 3HP treatment because of adverse events that were attributed to study medications (Table 8): 1 child developed grade 1 emesis after receiving crushed isoniazid tablets or the combination of crushed isoniazid and rifapentine, but the patient tolerated crushed rifapentine without emesis; and 2 adults developed grade 3 events (hypersensitivity in 1 patient and dyspnea in 1 patient). During the 24 hours after drug administration, no sign or symptom greater than grade 1 was identified in any patient in the present study.

DISCUSSION

The present study showed that of patients receiving rifapentine and isoniazid for the treatment of LTBI, children who received a geometric mean 2.1-fold increase in the milligram per kilogram dose of rifapentine had a 1.3-fold greater geometric mean rifapentine AUC0-inf and C24 compared to adults given a 900-mg treatment dose. Mean rifapentine AUC0-inf was significantly greater in children taking whole tablets than adults and greater in children taking whole tablets than children given crushed tablets. The children given crushed tablets were younger, had smaller body weight, and had been given a lower total dose and a higher milligram per kilogram dose than children given whole tablets. There was a 7-fold variation in rifapentine AUC0-inf in children. Even after adjustment for covariates, interindividual variability in this study was high (coefficient of variation of 40% for CL/F), although it was comparable to other studies of rifapentine. The causes of variability could be due to interindividual differences in bioavailability, pharmacogenomics, or other causes. Mean rifapentine AUC0-inf in this study (457 mcg × h/mL, fasting adults) was similar to mean rifapentine AUC0-inf obtained in 7 adults with once-weekly, continuation-phase TB therapy (472 mcg × h/mL, fasting, 900-mg dose) [8].

The present population pharmacokinetic model of once-weekly, orally administered rifapentine established that
Figure 4. Area under the concentration-time curve (AUC<sub>0-inf</sub>) of rifapentine (A) and rifapentine metabolite (B) in groups of patients divided (1) by dose from the weight bands used in the treatment algorithm and (2) by rifapentine tablet integrity (whole and crushed). The 25th, 50th, and 75th percentiles are indicated by the bottom, middle, and top, respectively of the rectangular boxes. The whiskers are drawn at either the minimum (maximum) or 1.5 times the interquartile range below (above) the 25th (75th) percentile depending on which of the 2 is closer to the median. The geometric means (X) and 90 percent CIs are indicated for each group.

Abbreviations: CI, confidence interval; GM, geometric mean.
Figure 5. Clearance maturation for rifapentine. Relation between rifapentine clearance and age: allometric scaling (tick line); estimated from the data (dashed line). A, Fraction of adult clearance normalized per kilogram body weight. B, Fraction of total adult clearance. Abbreviations: CL, clearance; CL/F, clearance corrected for bioavailability.
Table 6. Estimated Parameters for the Integrated Pharmacokinetic Model for Oral Rifapentine in Children and Adults With Latent Tuberculosis Infection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (RSE, %)</th>
<th>Between-Subject Variability, CV% (RSE, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CL/F}^a$ (L/h)</td>
<td>2.32 (11)</td>
<td>40 (13)</td>
</tr>
<tr>
<td>$\text{V/F}^b$ (L)</td>
<td>51.7 (10)</td>
<td>47 (15)</td>
</tr>
<tr>
<td>Correlation $\text{CL-V}$</td>
<td>0.758 (18)</td>
<td>-</td>
</tr>
<tr>
<td>$\text{ka}$ (h$^{-1}$)</td>
<td>1.69 (34)</td>
<td>-</td>
</tr>
<tr>
<td>Mean transit time (h)</td>
<td>0.62 (27)</td>
<td>90 (47)</td>
</tr>
<tr>
<td>Number of transit compartments</td>
<td>1.8 (76)</td>
<td>-</td>
</tr>
<tr>
<td>Maximal age-dependent increase in $\text{CL}$</td>
<td>0.22 (23)</td>
<td>-</td>
</tr>
<tr>
<td>$\text{Half-life (y)}$ for age-related change in $\text{CL/kg}$ to disappear</td>
<td>1.49 (38)</td>
<td>-</td>
</tr>
<tr>
<td>Decrease in $\text{F}$ with crushed tablet (fraction)</td>
<td>0.26 (36)</td>
<td>-</td>
</tr>
<tr>
<td>$\text{CLm/Fmd}$ (L/h)</td>
<td>2.05 (10)</td>
<td>64 (18)</td>
</tr>
<tr>
<td>$\text{Vm/Fme}$ (L)</td>
<td>21.87 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Correlation $\text{CL-CLm}$</td>
<td>0.88 (17)</td>
<td>-</td>
</tr>
<tr>
<td>Bioavailability of 900-mg dose</td>
<td>0.96 (19)</td>
<td>-</td>
</tr>
<tr>
<td>Bioavailability of 1200-mg dose</td>
<td>0.76 (16)</td>
<td>-</td>
</tr>
<tr>
<td>Food effect on bioavailability (fraction)</td>
<td>0.403 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Proportional residual error, rifapentine, children (CV%)</td>
<td>15 (10)</td>
<td>-</td>
</tr>
<tr>
<td>Additive residual error, rifapentine, children (mcg/mL)</td>
<td>0.62 (27)</td>
<td>-</td>
</tr>
<tr>
<td>Proportional residual error, metabolite, children (CV%)</td>
<td>14 (18)</td>
<td>-</td>
</tr>
<tr>
<td>Additive residual error, metabolite, children (mcg/mL)</td>
<td>0.47 (14)</td>
<td>-</td>
</tr>
<tr>
<td>Proportional residual error, rifapentine, adults (CV%)</td>
<td>29 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Proportional residual error, metabolite, adults (CV%)</td>
<td>31 (8)</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: CL, rifapentine oral clearance; CLm, clearance of 25-desacetyl-rifapentine; CV%, coefficient of variance; Effsize, maximal increase in $\text{CL/kg}$ observed at age of 2 years; F, bioavailability; Fm, fraction metabolized; ka, absorption rate constant; RSE, relative standard error; V, rifapentine volume of distribution.

$^a$$\text{CL/F}$ for a 70 kg patient; $\text{CL/F}$ for others is defined using the allometrically scaled relationship.

$^b$$\text{CLm/Fm}$ for a 70 kg patient; $\text{CLm/Fm}$ for others is defined using the allometrically scaled relationship.

$^c$Effsize parameter from equation 4.

$^d$$\text{V/F}$ for a 70 kg patient; $\text{V/F}$ for others is defined using the allometrically scaled relationship.

$^e$$\text{Vm/Fm}$ for a 70 kg patient; $\text{Vm/Fm}$ for others is defined using the allometrically scaled relationship.

Figure 6. Visual predictive check for blood levels of rifapentine (6A) and metabolite (6B) for different age groups. Solid black line represents median of observed data. The dotted black lines are 5th and 95th percentile of the observed data. Middle gray shaded area represents simulated median with uncertainty (for 500 repetitions of visual predictive check). The bottom and top of the gray shaded areas represent simulated 5th and 95th percentile, respectively, with uncertainty. Abbreviation: CL, clearance.
and adults in the study (Table 4). Food increased the bioavailability of rifampin by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine doses by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapten
LTBI, the recommended dose for adults is 900 mg and the maximum dose for children does not exceed 900 mg. The present study showed that crushing rifapentine tablets causes a 26% decreased bioavailability. This effect of tablet crushing on bioavailability in younger children may have confounded the effect of young age on CL/F. We evaluated the effects of these 2 covariates by analyzing subsets of children who could swallow the whole tablet. In addition, the ratio of clearance of rifapentine to clearance of metabolite showed a clear trend with age, suggesting increased metabolic activity in very young children.

In children or adults, the AUC0-inf of rifapentine and metabolite was similar (Table 5). The 25-desacetyl-rifapentine metabolite has activity against Mycobacterium tuberculosis. The minimum inhibitory concentration of rifapentine to susceptible strains of M. tuberculosis is 0.03–0.06 µg/mL and of 25-desacetyl-rifapentine is 0.125–0.25 µg/mL [17].

Higher milligram per kilogram rifapentine doses were well tolerated among young children. In the present study, there were no serious adverse events associated with rifapentine administration in children. The safety and tolerability of rifapentine in children were similar to concurrent adult controls in the present study. The frequency of treatment-related adverse events in the PREVENT TB trial was similar for children who participated in the present study and for those who did not (1.3% vs 1.8%) [18].

In this study, rifapentine concentration was measured once at 24 hours after drug administration to patients. This sparse sampling was done to maximize the number of outpatient children participants. The C24 time was chosen because of high correlations between rifapentine C24 and AUC in historical data from 3 pharmacokinetic studies in children and adults with intensive pharmacokinetic sampling [7, 8, 10] (Supplemental material, Table S1). In addition, cross-validation training or test analyses confirmed that C24 consistently predicted AUC (Supplemental material, Results; Table S2; Figures S1 and S2).

Most (83%–93%) rifapentine remains stable in different food mixtures [11]. In the present study, rifapentine and isoniazid were administered together, soon after crushing and mixing in a small volume of liquid or food, and this practice may have affected rifapentine exposure. Rifapentine undergoes pH-dependent decomposition; in the presence of isoniazid, rifapentine has maximum degradation of 30% at pH 2. Therefore, coadministration of crushed rifapentine and isoniazid tablets may have increased pH-dependent decomposition [19]. Food would have to be taken with rifapentine doses in children to attain similar rifapentine exposures found in this study, because food has a substantial effect on rifapentine bioavailability, as shown in this and other studies [13-16], and because most children (95%) and adults (79%) in this study took rifapentine with food. The present study showed decreased bioavailability of rifapentine with crushed tablets compared to whole tablets. In a previous study, children who received a crushed tablet had a similar maximum concentration but a significantly shorter time to peak level compared with children who received a whole tablet [7]. The lower systemic drug exposures in children who received crushed tablets suggest that better formulations of rifapentine are needed for children.

The PREVENT TB dosing algorithm for children resulted in higher rifapentine exposure in children than in adults. In 8 (10%) of 80 children, the geometric mean rifapentine AUC was >100% and <150% of the geometric mean AUC found in adults. In 7 (9%) children, rifapentine geometric mean AUC was <20% of the adult geometric mean AUC. Notwithstanding the higher rifapentine exposures found in children compared with adults, the rifapentine doses were well tolerated and safe in this study. In the phase 3

### Table 8. Adverse Events Reported in Patients Treated With Rifapentine and Isoniazid for Latent Tuberculosis Infection

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (y)</th>
<th>Reference Dose</th>
<th>Adverse Event</th>
<th>Grade</th>
<th>Causal Relationship</th>
<th>Drug Discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>8072</td>
<td>2</td>
<td>6</td>
<td>Sinusitis</td>
<td>2</td>
<td>Unlikely</td>
<td>No</td>
</tr>
<tr>
<td>7642</td>
<td>4</td>
<td>9</td>
<td>Decreased appetite</td>
<td>1</td>
<td>Unlikely</td>
<td>No</td>
</tr>
<tr>
<td>7143</td>
<td>4</td>
<td>3</td>
<td>Urinary tract infection</td>
<td>2</td>
<td>Not related</td>
<td>No</td>
</tr>
<tr>
<td>7362</td>
<td>23</td>
<td>3</td>
<td>Hypersensitivity</td>
<td>3</td>
<td>Definite</td>
<td>Yes</td>
</tr>
<tr>
<td>8017</td>
<td>27</td>
<td>3</td>
<td>Pregnancy</td>
<td>NA</td>
<td>Unclassifiable</td>
<td>No</td>
</tr>
<tr>
<td>7158</td>
<td>33</td>
<td>4</td>
<td>Dyspnoea</td>
<td>3</td>
<td>Definite</td>
<td>Yes</td>
</tr>
<tr>
<td>6972</td>
<td>36</td>
<td>4</td>
<td>Urinary tract infection</td>
<td>2</td>
<td>Not related</td>
<td>No</td>
</tr>
<tr>
<td>7397</td>
<td>41</td>
<td>7</td>
<td>Back pain</td>
<td>3</td>
<td>Not related</td>
<td>No</td>
</tr>
<tr>
<td>8001</td>
<td>42</td>
<td>5</td>
<td>Hyperkeratosis</td>
<td>2</td>
<td>Possible</td>
<td>No</td>
</tr>
<tr>
<td>7940</td>
<td>49</td>
<td>3</td>
<td>Joint swelling</td>
<td>2</td>
<td>Unlikely</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; PK, pharmacokinetic.

aN = 157 patients (80 children and 77 adults). There were 3 children who had adverse events (total, 4 adverse events in children) and 7 adults who had adverse events (total, 7 adverse events in adults).

bAdverse event attributed to study drug(s).

cUrticaria and angioedema.
PREVENT TB trial among all 473 children aged 2 to 17 years, the rifapentine doses from this algorithm were well tolerated and safe with a high frequency of completion and few serious adverse events [18]. None of the children treated with 3HP developed TB, and, in the efficacy analysis, 3HP was noninferior to 9 months of daily isoniazid.

In the pharmacokinetic study, because rifapentine exposure in children was found to be higher than that in adults, we developed alternate dosing algorithms (Table 7A–C) by NLME modeling that are anticipated to attain rifapentine exposures in children comparable to adults. However, limitations of these “modeled” dosing algorithms are as follows: (1) external validation of rifapentine AUC for the modeled doses have not been prospectively studied; and (2) the NLME modeling was based on children who came from more limited racial, geographic, and possibly pharmacogenomic diversity relative to the global pediatric TB population. Another caveat is that a definitive pharmacokinetic surrogate for rifapentine efficacy has not been determined. Because of interindividual variability of rifapentine exposures, the rifapentine exposures may be suboptimal in some patients with the modeled dose algorithm, ie, the mean rifapentine exposure found in American adults in this study may possibly not attain the ideal mean pharmacokinetic target for children.

CONCLUSIONS

In summary, this is the first pharmacokinetic evaluation of rifapentine at steady-state in children. The rifapentine doses used in the present study are supported by a number of factors including the following: (1) the relative exposure achieved in children compared to adults; (2) the high interindividual variability in rifapentine exposure; (3) the current availability of only the 150-mg rifapentine tablet for use in children; (4) the population pharmacokinetic model; and (5) the safety, tolerability, and efficacy profiles of children in the PREVENT TB trial [18]. The present study shows that rifapentine mean AUC_{0–inf} was higher in pediatric patients with LTBI who received the PREVENT TB weight-based dosing (ie, higher milligram per kilogram doses) than in adults who received a 900-mg dose. These higher rifapentine doses were clinically well tolerated in all 473 children in the phase 3 PREVENT TB treatment trial. Because of higher exposure among children, we developed alternate pediatric dosing algorithms based on NLME modeling for crushed and whole tablets. However, these model dose algorithms have not been prospectively assessed in pharmacokinetic or clinical outcomes studies. Use of higher weight-adjusted rifapentine doses for children aged 2 to 11 years are warranted to achieve systemic exposures that are associated with successful treatment of LTBI in adults [4]. Although the modeled dosing algorithm affords valuable insight regarding the dosing of crushed versus whole tablets, the PREVENT TB dosing algorithm was shown to be safe and effective in a clinical trial. Pending the evaluation of a pediatric formulation for rifapentine, we believe that clinicians treating children for LTBI with 3HP may consider either the PREVENT TB or the alternate modeled dosing algorithms when prescribing the tablet formulation of rifapentine.

Supplementary Data

Supplementary materials are available at the Journal of the Pediatric Infectious Diseases Society online (http://jpids.oxfordjournals.org). Supplementary materials consist of data provided by the author that were published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Acknowledgments

We thank Drs. Susan Dorman (Tuberculosis Trials Consortium), Andrew Vernon (Centers for Disease Control and Prevention), Marilyn Maroni (Access to Medicines - sanofi), and Christine Farenc (Access to Medicines - sanofi) for review of the manuscript; Lorna Bozeman for logistical support; and Elly Trepman for editing assistance.

Author contributions. M. W., W. R. M., S. M. A.-R., and G. L. K. designed the pharmacokinetic study. R. M. S. developed the population PK model. M. W., R. M. S., T. J. P., and J. A. L. G. performed statistical analyses. M. W. and R. M. S. had access to all data, interpreted the results, and wrote the manuscript. C. A. P. performed the rifapentine and metabolite concentrations for the PREVENT TB PK samples. The participating Tuberculosis Trials Consortium Study 26 clinical sites (principal investigators and study coordinators) (numbers of patients enrolled) were as follows: South Texas (Richard Wing MD, Marc Weiner MD, Josephina Gonzalez LVN, Diane Valenzuela LVN, Diane Wing RN) (67); University of North Texas Health Science Center (Stephen Weis DO, Le Turk RN, Barbara King RN) (45); University of Texas Health Science Center in San Antonio/South Texas Veterans Health Care System (Marc Weiner MD, Jose Jimenez BS, Hipolito Pavon MPH, Melissa Engle CRT CCRC (15); University of California Medical Center Los Angeles (Brenda Jones MD, Peregrina Molina RN) (12); Denver Health and Hospitals, (William Burman MD, Jan Tapy ANP RN, Laurie Luna RN, Grace Sanchez CCA) (10); Duke University Medical Center/Durham VA (Carol D Hamilton MD MHS, Emily Hecker MSN RN, Ann Mosher FNP MPH) (6); Vanderbilt University/Nashville VA (Timothy Sterling MD, Amy Kerrigan MSN RN CCRP, Belinda Redd LVN) (4); and Columbia University (Neil Schluger MD, Joseph Burzynski MD, MPH, Magda Wolk RN, Vilma Lozano) (3).

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. A contract between sanofi-aventis and the University of Texas Health Science Center at San Antonio in support of this study was reported by M. W. A contract between the Centers for Disease Control and Prevention,
sano-aventis, and Children’s Mercy Hospitals in support of pharmacokinetic studies was reported by G. L. K. R. M. S. and T. R. S. were consultants to sano-aventis.

**Financial support.** This work was supported by the Centers for Disease Control and Prevention through the Tuberculosis Trials Consortium; the Veterans Administration; and the National Institutes of Health’s National Center for Research Resources and the National Center for Advancing Translational Sciences (Award Number 8UL1TR000149).

**Potential conflicts of interest.** All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**