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Original Article

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

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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 $\geq$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.

Table 1. Rifapentine Dosing for Children With Latent Tuberculosis Infection in the Present Study[a]

Weight (kg)	Rifapentine Dose (mg)	Rifapentine Dose (mg/kg)	Age of Study Patients, y (mean ± standard deviation)
10–14	300	21–30	2.6 ± 0.8
>14–25	450	18–32	4.5 ± 1.6
>25–32	600	19–24	7.4 ± 2.2
>32–50	750	15–23	9.7 ± 2.4
>50	900	≤18	38.8 ± 12.9

[a]N = 80 children. Same dosing guideline was used for children in the PREVENT TB trial.

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

material, Methods) [12]. 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 ($AUC_{0\text{-inf}}$) 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).*

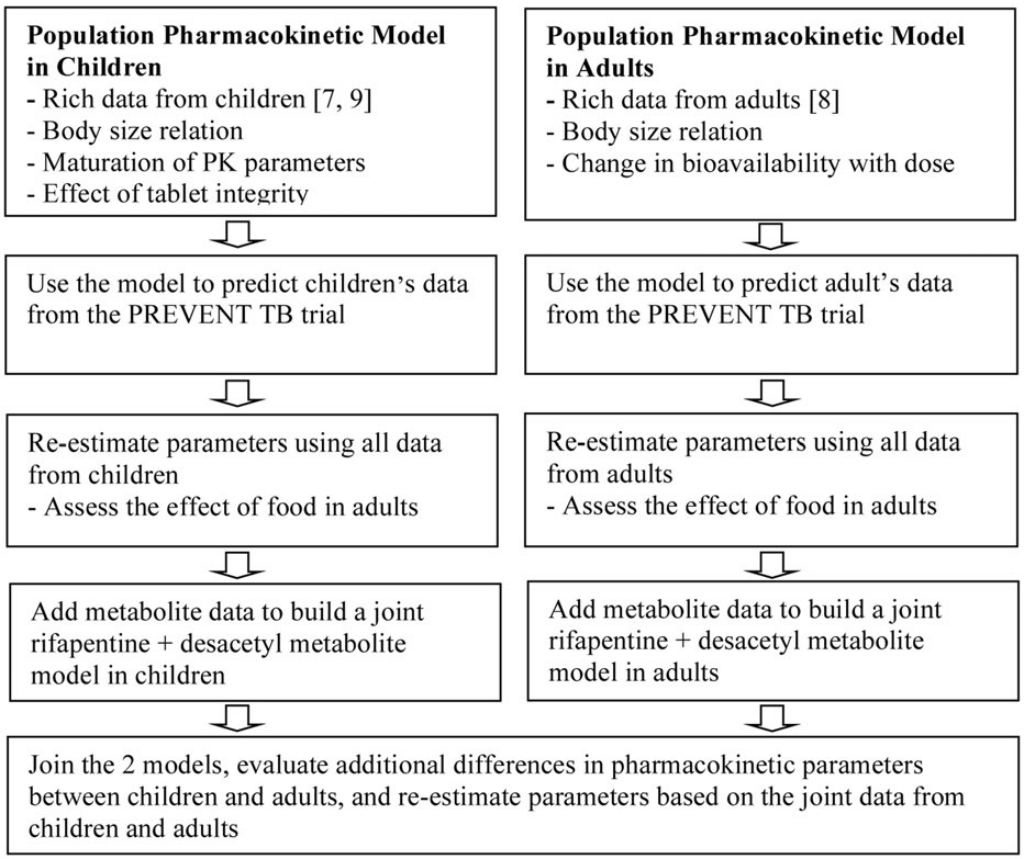

Figure 1. Modeling strategy for rifapentine and metabolite in children and adults treated for latent tuberculosis infection in the PREVENT TB trial. A detailed description of the pharmacokinetic modeling methodology is located in the Supplemental material (Methods). Abbreviations: PK, pharmacokinetic; TB, tuberculosis.

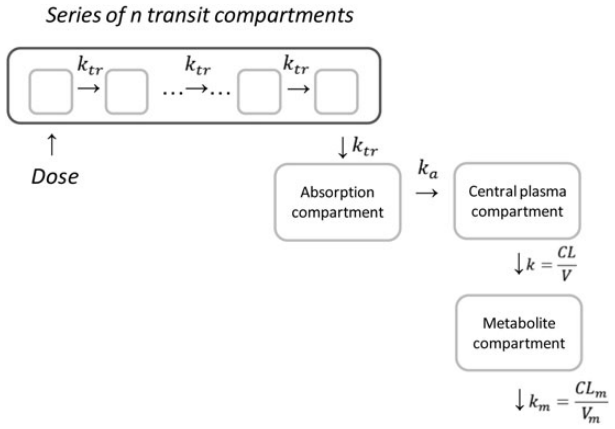

Figure 2. Rifapentine model structure. Abbreviations: CL, rifapentine clearance; CL_m, metabolite clearance; k, rifapentine elimination rate constant; k_a, absorption rate constant; k_m, metabolite elimination rate constant; k_{tr}, transit rate constant; n, number of transit compartments; V, rifapentine volume distribution; V_m, metabolite volume of distribution.

Data Analysis

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 χ^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 $AUC_{0\text{-inf}}$ and C24 were respectively 31% and 28% greater in children than adults (Table 5; Figure 3). In children, the rifapentine geometric mean $AUC_{0\text{-inf}}$ was significantly greater with whole versus crushed tablets, and $AUC_{0\text{-inf}}$ 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 $AUC_{0\text{-inf}}$ >80% of the geometric mean rifapentine $AUC_{0\text{-inf}}$ of all adults in the present study. The geometric mean $AUC_{0\text{-inf}}$ 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

Equation No.	Description	Equation
1	Rifapentine absorption kinetics	$\frac{dA_1}{dt} = \frac{F \times Dose \times k_{tr} \times (k_{tr} \times t)^n \times e^{(-k_{tr} \times t)}}{n!} - k_a \times A1$
2	Rifapentine disposition kinetics	$\frac{dA_2}{dt} = k_a \times A1 - \frac{CL}{V} \times A2$
3	25-Desacetyl-rifapentine disposition kinetics	$\frac{dA_3}{dt} = \frac{CL}{V} \times A2 - \frac{CLM}{VM} \times A3$
4	Rifapentine CL and its relationship with age and weight	$CL = TVCL \times \left(1 - Effsize + Effsize \times e\left[-(Age - 2) \times \frac{\ln(2)}{MatHL}\right]\right) \times \left(\frac{WT}{WT_{median}}\right)^{0.75}$
5	25-Desacetyl-rifapentine clearance	$CLm = TVCLm * \left(\frac{WT}{WT_{median}}\right)^{0.75}$
6	Rifapentine central volume	$Vc = TVVc * \left(\frac{WT}{WT_{median}}\right)^{1}$
7	25-Desacetyl-rifapentine central volume	$Vm = TVVm * \left(\frac{WT}{WT_{median}}\right)^{1}$
		$F = 1$
8	Bioavailability expression and its relationship to dose, crushing, and food	$if\ tablet = crushed,\ F = 1 + \theta_{crushed}, \theta_{crushed} = decrease\ in\ F\ by\ crushing\ the\ tablet$
		$if\ Dose = 900\,mg,\ F = \theta_{900\,mg} = Relative\ bioavailbility\ for\ 900\,mg\ dose$
		$if\ Dose = 1200\,mg,\ F = \theta_{1200\,mg} = Relative\ bioavailbility\ for\ 1200\,mg\ dose$
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; k_a, absorption rate constant; k_{tr}, 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.

Table 3. Relation Between Patient Age and Rifapentine Dose in Children and Adults in the Present Study[a]

Patients	Number of Subjects	Rifapentine Dose (mg/kg)
All children	80	23.2 (4.3)
Age 2–4 y	40	25.8 (3.4)
Age 5–8 y	22	22.3 (3.2)
Age 9–11 y	18	18.6 (2.9)
Adults, all (age >18 y)	77	11.0 (2.5)

[a]N = 80 children and 77 adults. Data reported as mean ± standard deviation.

Table 4. Demographic and Clinical Features of Children and Adults in the Present Study[a]

Feature	Children	Adults	*P* Value[b]
Number subjects	80	77	
Age, median (range), y	4.5 (2–11)	40 (19–63)	<.001
Race			.50
Black, n (%)	11 (14)	16 (21)	
White, n (%)	65 (81)	57 (74)	
Asian, n (%)	4 (5)	4 (5)	
Ethnicity, Hispanic	68 (85)	54 (70)	.03
Gender, male, n (%)	41 (51)	40 (52)	.93
HIV infection, n (%)[c]	0 of 5	1 of 54 (2)	
Drug administration			
Whole tablets, n (%)	25 (31)[d]	77 (100)	<.001
With food, n (%)	70 (88)	53 (69)	.005

Abbreviation: HIV, human immunodeficiency virus.
[a]Present study was the pharmacokinetic component of the PREVENT TB trial [4]. Data reported as number (%) or median (range, minimum to maximum).
[b]χ^2 for categorical variables and Mann-Whitney rank for the continuous variable.
[c]Only 5 children and 54 adults were tested for HIV infection.
[d]Children who could not swallow whole tablets and received crushed tablets (n = 55 [69%]) were significantly younger than children who could swallow whole tablets (n = 25 [31%]) (mean age: crushed tablets, 5 y; whole tablets 7 y; $P < .01$).

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; $P \leq .001$). 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 7*A*). Modeled rifapentine doses were then estimated for use with whole tablets (Table 7*B*)

Table 5. Pharmacokinetic Parameters of Rifapentine and Metabolite (25-Desacetyl-rifapentine) in Children and Adults[a]

	Children			Adults
Rifapentine	All children	Whole tablet administration	Crushed tablet administration	
Number of subjects	80	25	55	77
Dose (mg/kg)	22.8 (21.9, 23.7) [**23.1 {16.3, 30}**]	21.2 (19.8, 22.8) [**22.5 {15.8, 27.8}**]	23.5 (22.4, 24.7) [**23.1 {16.9, 30}**]	10.7 (10.3, 11.2) [**11.1 {7.3, 15.6}**]
Dose, ratio GM vs adults	2.12 (2.00, 2.25)[b]	1.98 (1.82, 2.15)[b]	2.19 (2.06, 2.33)[b]	
$AUC_{0\text{-inf}}$ (mcg × h/mL)	720 (674, 769) [**759 {375, 1186}**]	884 (789, 991) [**872 {559, 1284}**]	656 (607, 708) [**657 {368, 1095}**]	551 (516, 588) [**553 {326, 931}**]
$AUC_{0\text{-inf}}$ ratio GM vs adults	1.31 (1.19, 1.44)[b]	1.60 (1.41, 1.83)[b]	1.19 (1.08, 1.32)[b]	
C24 (mcg/mL)	10.9 (10.0, 12.0) [**12.4 {3.7, 20.3}**]	14.1 (12.1, 16.6) [**14.1 {8.2, 23.1}**]	9.7 (8.7, 10.8) [**10.4 {3.1, 19.4}**]	8.5 (7.8, 9.3) [**8.3 {4.4, 17.1}**]
C24, ratio GM vs adults	1.28 (1.12, 1.46)[b]	1.66 (1.38, 1.99)[b]	1.14 (0.99, 1.31)[c]	
25-Desacetyl-rifapentine metabolite				
$AUC_{0\text{-inf}}$ (mcg × h/mL)	735.0 (672, 804) [**800 {337, 1436}**]	843.4 (720, 988) [**877 {438, 1393}**]	690.5 (621, 768) [**629 {305, 1465}**]	521 (476, 570) [**484 {235, 1088}**]
$AUC_{0\text{-inf}}$ ratio GM vs adults	1.41 (1.24, 1.60)[b]	1.62 (1.35, 1.94)[b]	1.33 (1.15, 1.52)[b]	

Abbreviations: $AUC_{0\text{-inf}}$ area under the concentration-time curve (from 0 to time infinity); C24, concentration at 24 hours after drug administration; GM, geometric mean.
[a]Data are reported as geometric mean (90% confidence interval) and [**median {5th, 95th percentile}**] or ratio geometric mean (90% confidence interval).
[b]Comparison of children vs adults: $P \leq .01$.
[c]$P > .05$.

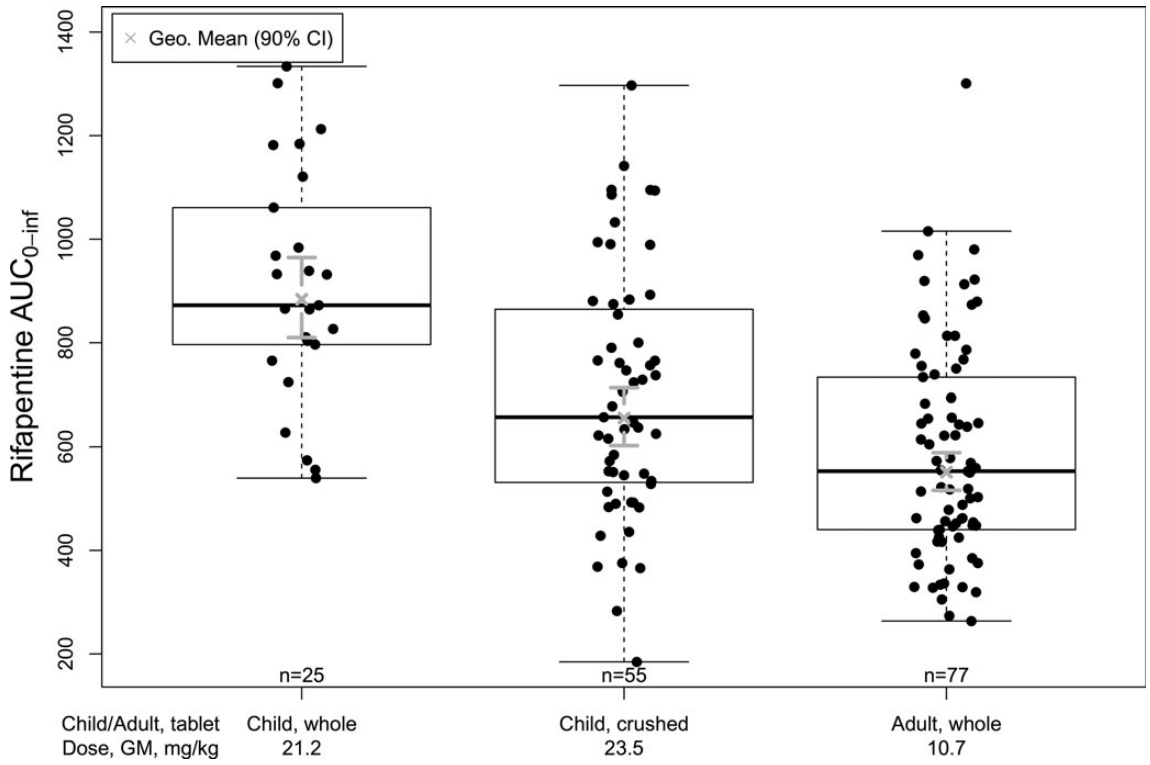

Figure 3. Rifapentine $AUC_{0\text{-inf}}$ in adults and in children divided by tablet integrity (crushed or whole). The 25th, 50th, and 75th percentiles are indicated by the bottom, middle, and top, respectively, of the rectangular boxes. The whiskers are drawn at either the minimum (maximum) or 1.5 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% CIs are indicated for each patient group. Abbreviations: $AUC_{0\text{-inf}}$, area under concentration-time curve from 0 to time infinity; CI, confidence interval; GM, geometric mean.

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 $AUC_{0\text{-inf}}$ and C24 compared to adults given a 900-mg treatment dose. Mean rifapentine $AUC_{0\text{-inf}}$ 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 $AUC_{0\text{-inf}}$ 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 $AUC_{0\text{-inf}}$ in this study (457 mcg × h/mL, fasting adults) was similar to mean rifapentine $AUC_{0\text{-inf}}$ 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

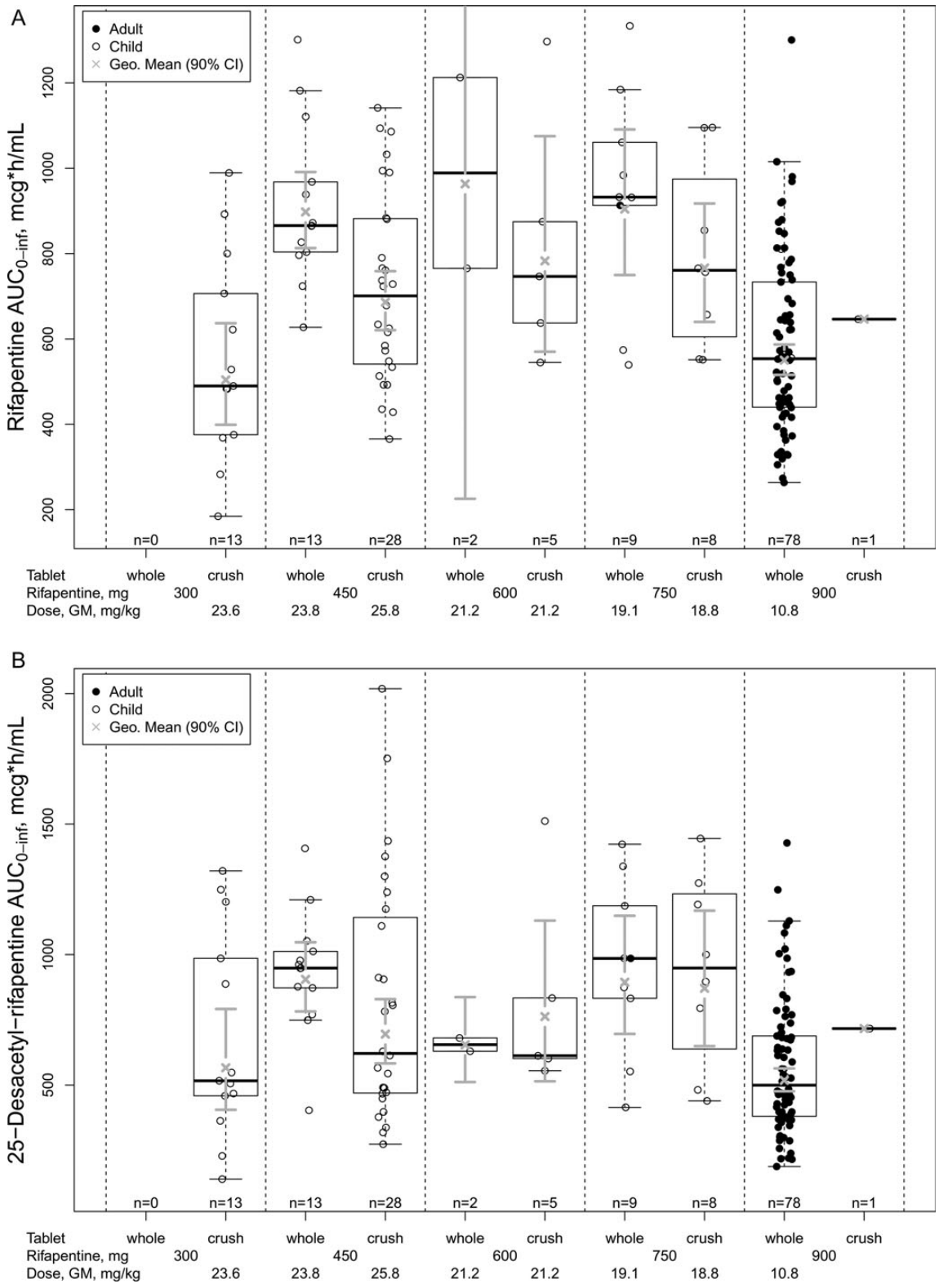

Figure 4. Area under the concentration-time curve ($AUC_{0\text{-}inf}$) of rifapentine (*A*) and rifapentine metabolite (*B*) in groups of patients divided (1) by dose from the weight bands used in the treatment algorithm and (2) by rifapentine tablet integrity (whole and crushed). The 25th, 50th, and 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.

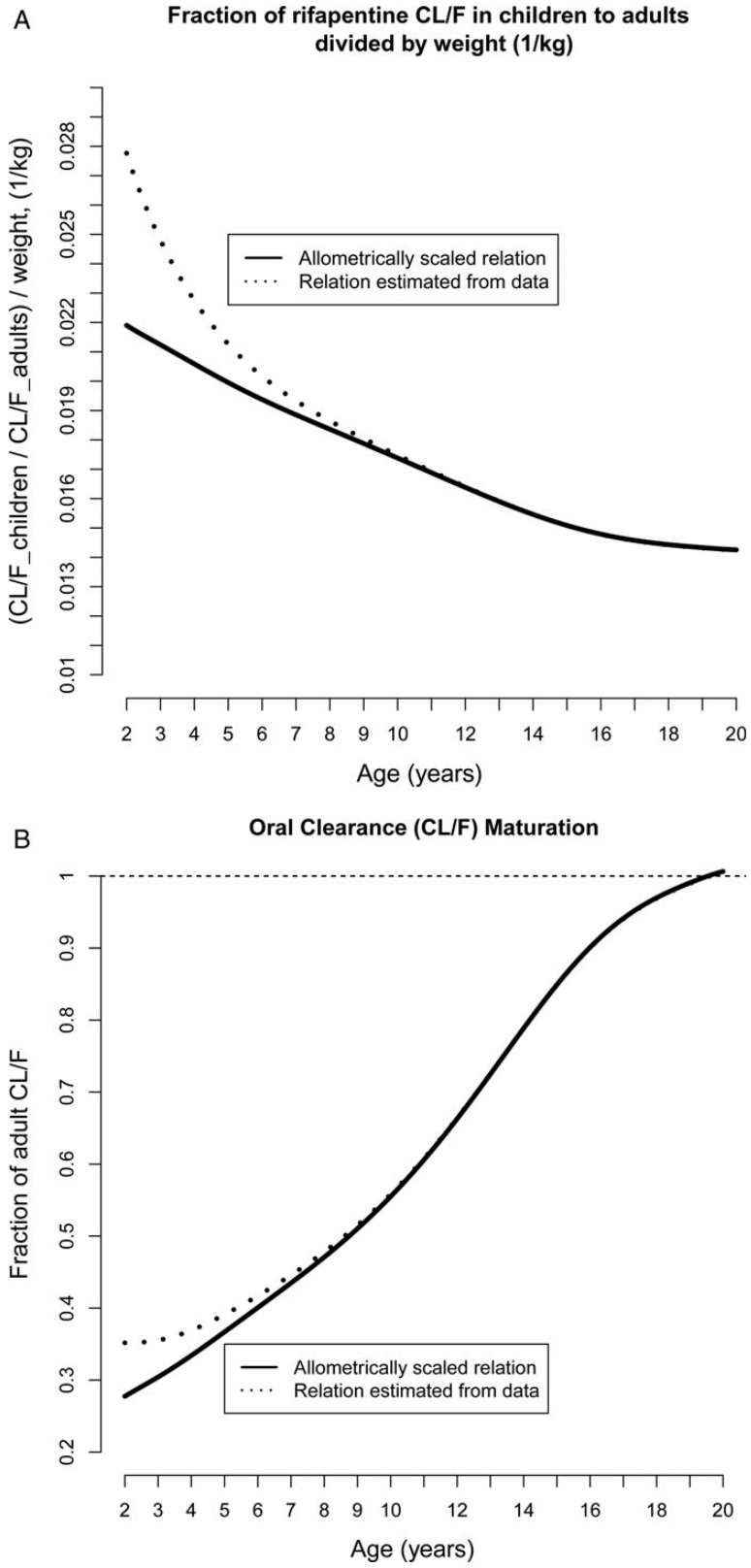

Figure 5. Clearance maturation for rifapentine. Relation between rifapentine clearance and age: allometric scaling (tick line); estimated from the data (dashed line). *A*, Fraction of adult clearance normalized per kilogram body weight. *B*, Fraction of total adult clearance. Abbreviations: CL, clearance; 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

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

Abbreviations: CL, rifapentine oral clearance; CLm, clearance of 25-desacetyl-rifapentine; CV%, coefficient of variance; Effsize, maximal increase in 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]CL/F for a 70 kg patient; CL/F for others is defined using the allometrically scaled relationship.
[b]CLm/Fm for a 70 kg patient; CLm/Fm for others is defined using the allometrically scaled relationship.
[c]Effsize parameter from equation 4.
[d]V/F for a 70 kg patient; V/F for others is defined using the allometrically scaled relationship.
[e]Vm/Fm for a 70 kg patient; Vm/Fm for others is defined using the allometrically scaled relationship.

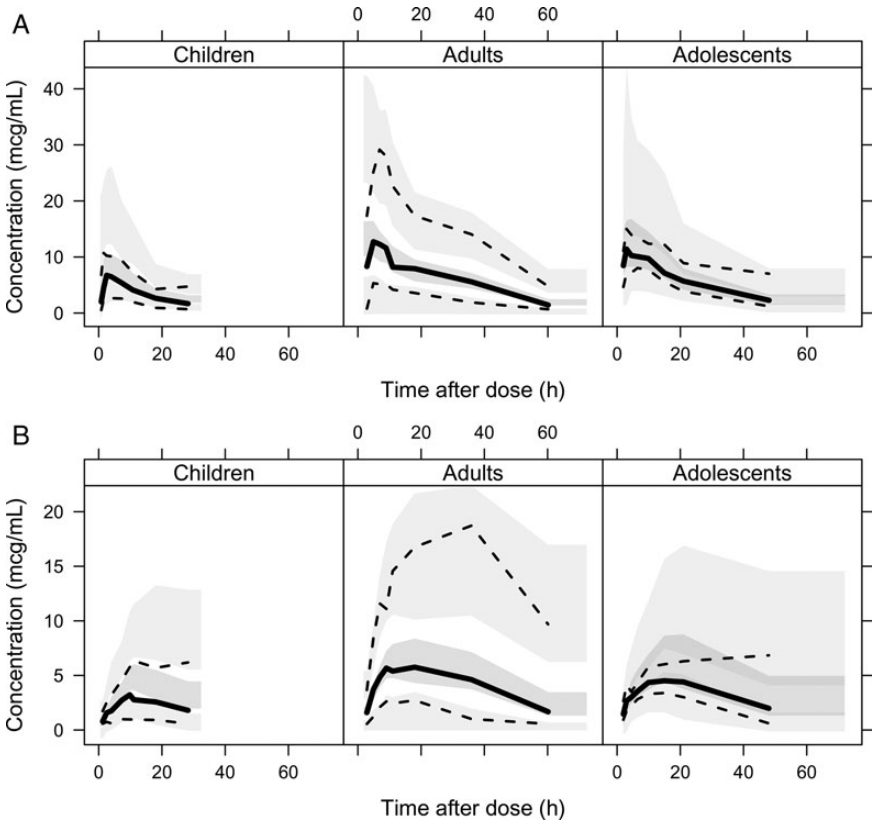

Figure 6. Visual predictive check for blood levels of rifapentine (6A) and metabolite (6B) for different age groups. Solid black line represents median of observed data. The dotted black lines are 5th and 95th percentile of the observed data. Middle gray shaded area represents simulated median with uncertainty (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.

Table 7*A*. Alternate Rifapentine Dosing Algorithms Derived From NLME Modeling[a]

Age (y)	Percentile Weight (kg)[b]								
	P3	p5	p10	p25	p50	p75	p90	p95	p97
2	10.0	10.2	10.6	11.2	12.1	13.0	13.9	14.6	15.0
2.5	10.7	11.0	11.4	12.1	13.0	14.1	15.2	16.0	16.5
3	11.4	11.7	12.1	12.9	13.9	15.2	16.5	17.4	18.0
3.5	12.1	12.3	12.8	13.7	14.9	16.3	17.8	18.8	19.6
4	12.8	13.1	13.6	14.6	15.9	17.4	19.2	20.4	21.3
4.5	13.5	13.9	14.4	15.5	16.9	18.7	20.6	22.0	23.1
5	14.3	14.7	15.3	16.5	18.0	20.0	22.1	23.8	24.9
5.5	15.2	15.6	16.2	17.5	19.2	21.3	23.7	25.5	26.9
6	16.0	16.4	17.1	18.5	20.3	22.7	25.4	27.4	28.9
6.5	16.9	17.3	18.1	19.6	21.6	24.1	27.1	29.4	31.1
7	17.7	18.2	19.1	20.7	22.9	25.7	29.0	31.5	33.4
7.5	18.6	19.2	20.1	21.8	24.3	27.4	31.0	33.8	35.8
8	19.5	20.1	21.2	23.1	25.8	29.2	33.2	36.2	38.5
8.5	20.5	21.2	22.3	24.4	27.4	31.1	35.6	38.9	41.4
9	21.6	22.3	23.5	25.9	29.1	33.3	38.2	41.8	44.6
9.5	22.7	23.5	24.9	27.5	31.0	35.6	40.9	44.9	47.9
10	24.0	24.9	26.3	29.2	33.1	38.0	43.9	48.2	51.4
10.5	25.4	26.3	27.9	31.0	35.2	40.6	46.9	51.5	55.1
11	26.8	27.8	29.5	32.9	37.4	43.2	49.9	55.0	58.7
11.5	28.4	29.5	31.3	34.8	39.6	45.8	53.0	58.3	62.4

Abbreviations: AUC, area under concentration-time curve; p3, 3rd percentile; p5, 5th percentile; pN, Nth percentile.

[a]Percentile weight of children by age (y) and weight (kg) are first estimated in this table. The rifapentine dose (mg) is then identified from the percentile weight and age for administration of whole tablets (Table 7*B*) or crushed tablets (Table 7*C*). The alternate dosing algorithm (Table 7*A*–*C*) derived by NLME modeling are anticipated to attain rifapentine exposures in children comparable to adults. However, limitations of the modeled dosing algorithms are that external validation of rifapentine AUC for the modeled doses has not been further evaluated in prospective clinical or pharmacokinetic studies.

[b]Percentile weight is identified from age and weight of a child. Then, the modeled rifapentine dose for administration of whole tablets (Table 7*B*) or crushed tablets (Table 7*C*) are identified from the percentile weight and age. By NLME modeling in this algorithm, the same weight and age are used for both boys and girls. The actual weight percentiles for age by weight were reported for girls [21].

Table 7*B*. The Modeled Algorithm Estimates for Whole Tablet Administration of Rifapentine Dose (mg) by Age and Percentile Weight[a]

Age (y)	Whole Tablet Dose (mg) of Rifapentine by Percentile Weight (Table 7A)								
	p3	p5	p10	p25	p50	p75	p90	p95	p97
2	300	300	300	300	300	300	300	300	300
2.5	300	300	300	300	300	300	300	300	300
3	300	300	300	300	300	300	300	300	450
3.5	300	300	300	300	300	300	300	450	450
4	300	300	300	300	300	300	450	450	450
4.5	300	300	300	300	300	300	450	450	450
5	300	300	300	300	300	450	450	450	450
5.5	300	300	300	300	300	450	450	450	450
6	300	300	300	300	300	450	450	450	450
6.5	300	300	300	300	450	450	450	450	450
7	300	300	300	300	450	450	450	450	600
7.5	300	300	300	450	450	450	450	600	600
8	300	300	300	450	450	450	600	600	600
8.5	300	300	450	450	450	450	600	600	600
9	450	450	450	450	450	450	600	600	600
9.5	450	450	450	450	450	600	600	600	750
10	450	450	450	450	450	600	600	750	750
10.5	450	450	450	450	600	600	600	750	750
11	450	450	450	450	600	600	750	750	750
11.5	450	450	450	600	600	600	750	750	900

Abbreviations: p3, 3rd percentile; p5, 5th percentile; pN, Nth percentile.

[a]The percentile weight is identified in Table 7*A* by age (y) and weight (kg).

Table 7*C*. The Modeled Algorithm Estimates for Crushed Tablet Administration of the Rifapentine Dose (mg) by Age and Percentile Weight[a]

Age (y)	Crushed Tablet Dose (mg) of Rifapentine by Percentile Weight (Table 7A)								
	p3	p5	p10	p25	p50	p75	p90	p95	p97
2	300	300	450	450	450	450	450	450	450
2.5	300	300	450	450	450	450	450	450	450
3	300	300	450	450	450	450	450	450	450
3.5	300	450	450	450	450	450	450	450	600
4	450	450	450	450	450	450	450	600	600
4.5	450	450	450	450	450	450	600	600	600
5	450	450	450	450	450	450	600	600	600
5.5	450	450	450	450	450	600	600	600	600
6	450	450	450	450	450	600	600	600	600
6.5	450	450	450	450	450	600	600	600	750
7	450	450	450	450	600	600	600	750	750
7.5	450	450	450	450	600	600	750	750	750
8	450	450	450	600	600	600	750	750	750
8.5	450	450	450	600	600	600	750	750	900
9	450	450	600	600	600	750	750	900	900
9.5	600	600	600	600	600	750	750	900	900
10	600	600	600	600	750	750	900	900	900
10.5	600	600	600	600	750	750	900	900	1050
11	600	600	600	750	750	900	900	1050	1050
11.5	600	600	600	750	750	900	1050	1050	1050

Abbreviations: p3, 3rd percentile; p5, 5th percentile; pN, Nth percentile.

[a]The percentile weight is identified in Table 7*A* by age (y) and weight (kg).

clearance scaled for size is higher in children than adults. The higher clearance in children per kilogram of body weight was anticipated. However, the youngest children had greater clearance per kilogram body weight compared with that anticipated from allometry (Figure 5). The additional relation, a nonlinear function of age, established that there was an additional increase in oral clearance per kilogram body weight of 21% for the youngest child (age, 2 y) compared with that expected from allometry (Figure 5). This difference disappeared with increased age, with an estimated half-life of 1.5 years. Allometry was sufficient to explain the relation between clearance and growth in children aged ≥ 9 years.

Compared with fasting conditions, rifapentine AUC is increased by 33% to 86% when the drug is taken with food [13–16]. Rifapentine AUC is increased by bulk with a low-fat meal and increased 46% by bulk with a high-fat meal [16]. Food consumption was not restricted in the present study, and food was consumed by most children and adults in the study (Table 4). Food increased rifapentine bioavailability by 40%. In addition, the pharmacokinetic model demonstrated that an increase in rifapentine dose >900 mg resulted in 24% decreased bioavailability, consistent with results of an earlier study of high doses of daily rifapentine [20]. For treatment of

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

Patient No.	Age (y)	Reference Dose No. for PK Sample	Adverse Event	Grade	Causal Relationship[b]	Drug Discontinued Because of Adverse Event
8072	2	6	Sinusitis	2	Unlikely	No
7642	4	9	Decreased appetite	1	Unlikely	No
7143	4	3	Urinary tract infection	2	Not related	No
		3	Drug intolerance	1	Definite	Yes
7362	23	3	Hypersensitivity[c]	3	Definite	Yes
8017	27	3	Pregnancy	NA	Unclassifiable	No
7158	33	4	Dyspnoea	3	Definite	Yes
6972	36	4	Urinary tract infection	2	Not related	No
7397	41	7	Back pain	3	Not related	No
8001	42	5	Hyperkeratosis	2	Possible	No
7940	49	3	Joint swelling	2	Unlikely	No

Abbreviations: NA, not applicable; PK, pharmacokinetic.
[a]N = 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).
[b]Adverse event attributed to study drug(s).
[c]Urticaria and angioedema.

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 $AUC_{0\text{-inf}}$ 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

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 7*A*–*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 $AUC_{0\text{-inf}}$ 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.

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