Pharmacokinetics of Rifapentine at 600, 900, and 1,200 mg during Once-Weekly Tuberculosis Therapy

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The pharmacokinetics of rifapentine at 600, 900, and 1,200 mg were studied during once-weekly continuation phase therapy in 35 patients with tuberculosis. Mean area under the plasma concentration–time curve ($AUC_{0-\infty}$) increased significantly with dose (rifapentine $AUC_{0-\infty}$: 296, 410, and 477 μg · hour/ml at 600, 900, and 1,200 mg, respectively; $p = 0.02$ by linear regression). In multivariate stepwise regression analyses, $AUC_{0-\infty}$ values for rifapentine and the active 25-desacetyl metabolite were associated with drug dose and plasma albumin concentration, and were lower among men and among white individuals. Fifty-four percent of patients had total (free and protein-bound) plasma concentrations of rifapentine and of desacetyl rifapentine detected for more than 36 hours after clearance of concurrently administered isoniazid. Serious adverse effects of therapy in these study patients were infrequent (1 of 35 cases; 3%) and not linked with higher rifapentine $AUC_{0-\infty}$ or peak concentration. The present pharmacokinetic study supports further trials to determine the optimal rifapentine dose for treatment of tuberculosis.

Keywords: pharmacokinetics; rifapentine; treatment; tuberculosis

Guidelines for treatment of tuberculosis from the Centers for Disease Control and Prevention, the American Thoracic Society, and the Infectious Diseases Society of America recommend the use of rifapentine, 600 mg in a once-weekly continuation phase regimen, for patients with noncavitary tuberculosis, with a sputum sample that is negative for acid-fast bacilli by smear at 2 months of therapy, and without human immunodeficiency virus (HIV) infection (1). The long half-life of rifapentine allows once-weekly dosing, resulting in a substantial decrease in the number of treatment encounters between the health care provider and patient receiving directly observed therapy (1). However, the treatment indication for once-weekly rifapentine and isoniazid was restricted, because rates of treatment failure or relapse with rifapentine at doses of 600–750 mg were unacceptable among patients with more severe pulmonary tuberculosis (2–5).

Three lines of evidence suggest that higher doses of rifapentine may improve efficacy. First, a murine model of tuberculosis demonstrated greater rifapentine efficacy at doses equivalent to 10 to 15 mg/kg in humans, compared with 5 mg/kg (6). Second, rifapentine is highly protein bound (96 to 99%), resulting in lower concentrations of biologically active, unbound drug at the site of infection (7). Therefore, higher doses than predicted may be necessary to achieve effective concentrations of unbound drug. Finally, in early dose-ranging clinical tuberculosis trials of another rifamycin, rifampin (8), the 450-mg dose was demonstrated to have decreased efficacy compared with the 600-mg dose. Thus, Phase II and III dose range safety, pharmacokinetic, and dose–response studies were initiated to better delineate the optimal rifapentine dose. Because no clinical study of repeated higher rifapentine doses had been conducted, the Tuberculosis Trials Consortium (TBTC)/United States Public Health Service evaluated the tolerability of rifapentine at 600, 900, and 1,200 mg in a prospective, randomized double-blind study in the continuation phase of tuberculosis treatment (9). In the present study, isoniazid, rifapentine, and 25-desacetyl rifapentine pharmacokinetics were determined in 35 patients enrolled in the tolerability trial. Some of this work was reported in the form of abstracts (10–12).

METHODS

TBTC Study 25 was a prospective, double-blind, randomized Phase II trial to evaluate the tolerability of once-weekly, continuation phase, directly observed therapy with rifapentine at three doses (600, 900, and 1,200 mg) and of isoniazid in 150 HIV-seronegative patients with drug-susceptible tuberculosis (9). The primary analysis of the present substudy was conducted with 35 patients enrolled in the Phase II study. Patients were administered the study drugs while fasting. A baseline blood sample before drug administration was obtained. After an oral rifapentine dose of 600, 900, or 1,200 mg, and isoniazid at 15 mg/kg, blood samples were collected at 2, 4, 6, 8, 10, 12, 18, 24, 48, and 72 hours.

The study was reviewed and approved by the Institutional Review Boards at the Centers for Disease Control and Prevention and at each of the nine participating research centers. All participants provided informed consent.

Analyses of total (protein-bound plus unbound) drug concentrations were performed using standard techniques (13). Analyses of pharmacokinetic parameters were performed using noncompartmental techniques (WinNonlin PK software, version 4; Pharsight, Mountain View, CA). "Drug exposure" was defined as the area under the concentration–time curve ($AUC_{0-\infty}$).

The null hypothesis was that rifapentine $AUC_{0-\infty}$ was unrelated to dose of rifapentine (between 600 mg [Food and Drug Administration–approved dose], 900 mg, and 1,200 mg). Data analyses were performed with software from SAS (Cary, NC). Differences between two groups (in Table 1) were determined by *t* test for continuous variables (with

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TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF TUBERCULOSIS PATIENTS IN THE PHARMACOKINETIC STUDY COMPARED WITH ALL OTHERS IN RANDOMIZED STUDY OF RIFAPENTINE TOLERABILITY

Variable	In PK Study (*n* = *35*)	Not in PK Study (*n* = *115*)	p Value†
Age, mean (SD), yr	42.8 (12.8)	44.8 (14.9)	0.49
Sex, male	23 (66)	88 (77)	0.27
Race/ethnicity			
White, non-Hispanic	9 (26)	22 (19)	0.47
White, Hispanic	11 (31)	14 (12)	0.02
Black	13 (37)	48 (42)	0.70
Asian and other race/ethnicities	2 (6)	31 (27)	0.009
Alcohol consumption*	16 (46)	42 (37)	0.33
Illicit injection drug use	4 (11)	7 (6)	0.28
Weight at PK study, mean (SD), kg	65.7 (11.9)	66.2 (13.1)	0.86
Culture for *M. tuberculosis* positive after 2 months of treatment	12 (34)	12 (10)	0.003
Bilateral infiltrates on X-ray	12 (39)	56 (50)	0.25
Cavity on X-ray	14 (44)	59 (53)	0.42
Rifapentine dose			0.13
600 mg	15 (43)	37 (32)	
900 mg	7 (20)	44 (38)	
1,200 mg	13 (37)	34 (30)	
Adverse events	11 (31)	33 (29)	0.83

Definition of abbreviation: PK = pharmacokinetic.
Unless otherwise specified, values present are n (%).
* Any alcohol consumption in month before Study 25 enrollment.
† p Value by *t* test for continuous variables and by Fisher exact test (2 × 2) or χ^2 for nominal variables.

a normal distribution) or Fisher exact test (2 × 2) and χ^2 for nominal variables. Data were natural log transformed if a normal distribution was rejected by the Shapiro–Wilk test or if variances of different groups were unequal and natural log transformation improved the validity of the analyses. Natural log-transformed results were back transformed to the original scale to obtain means and 95% confidence intervals. Between-dose comparisons of rifapentine drug $AUC_{0-\infty}$ were evaluated by regression analysis. Differences between groups or correlations between covariates and outcome were considered statistically significant at a $p < 0.05$. Multivariate regression analyses for the dependent variable rifapentine $AUC_{0-\infty}$ used a stepwise procedure for demographic, clinical, and laboratory covariables with a probability < 0.20 in bivariate analysis of each covariable adjusted for rifapentine dose. Chest radiograph findings were identified at baseline and after 2 months of the initial phase of therapy; alanine aminotransferase level (units per liter) was obtained at enrollment in TBTC Study 25; and body weight, body mass index, and albumin concentration were obtained at the time of pharmacokinetic sampling. Multivariate regression analyses for desacetyl rifapentine $AUC_{0-\infty}$ used a similar procedure.

Models for active, free plasma rifapentine and for free desacetyl rifapentine concentrations relative to the minimum inhibitory concentrations (MIC) of *Mycobacterium tuberculosis* were estimated as follows. Two and 6.9% of total plasma concentrations of rifapentine and desacetyl rifapentine, respectively, were assumed to be unbound to protein at each time point (14), and the estimate of free drug concentrations were divided by the MIC for *M. tuberculosis* (rifapentine MIC, 0.05 μg/ml; desacetyl rifapentine MIC, 0.25 μg/ml [15, 16]).

RESULTS

Demographic and clinical characteristics of the 35 HIV-seronegative patients with tuberculosis in the pharmacokinetic substudy were similar to those of the 115 other patients in the TBTC tolerability study of higher doses of rifapentine (Table 1). By chance, a greater percentage of patients with *M. tuberculosis* isolated from sputum cultures after 2 months of therapy participated in the pharmacokinetic study (12 of 35 [34%] versus 12 of 115 [10%]; p = 0.003). Also, fewer Asians and more Hispanics participated in the present study. Other demographic and clinical variables did not significantly differ.

Rifapentine plasma concentrations rose with dose (Figure 1). For example, the mean rifapentine maximum concentration (Cmax) increased from 12.2 μg/ml with the 600-mg dose to 14.6 μg/ml with the 900-mg dose and to 18.6 μg/ml with the 1,200-mg dose (Table 2). Mean rifapentine area under the plasma concentration–time curve ($AUC_{0-\infty}$) increased 1.39- and 1.61-fold as dose increased from 600 to 900 mg and to 1,200 mg, respectively (Table 2). The mean half-life ranged from 14.4 to 16.4 hours across doses.

At all administered doses, median rifapentine $AUC_{0-\infty}$ and Cmax were lower in white subjects compared with nonwhite subjects (Figure 2A and Table 3) and in males compared with females (Figure 2B and Table 3). In multivariate stepwise regression analyses, rifapentine $AUC_{0-\infty}$ was associated with drug dose and plasma albumin concentration and was lower among men and white individuals (Table 4). The 25-desacetyl metabolite $AUC_{0-\infty}$ was associated with the same four variables (dose, race, sex, and plasma albumin concentration; Table 4).

There was no apparent association between isoniazid pharmacokinetic parameters and the dose of coadministered rifapentine. The mean (SD) isoniazid area under the plasma concentration–time curve (AUC_{0-12}) and Cmax were 55 (24), 43 (14), and 45 (26) μg · hour/ml and 11.4 (3.2), 10.9 (2.6), and 10.6 (4.5) μg/ml at rifapentine doses of 600, 900, and 1,200 mg, respectively. The differences in isoniazid AUC_{0-12} and maximum concentration were not significantly different between rifapentine doses (AUC_{0-12}, p = 0.26; Cmax, p = 0.51).

The occurrence of study adverse events was not associated with elevated rifapentine area under the concentration–time curve (mean $AUC_{0-\infty}$, 321 μg · hour/ml for 10 cases with any adverse events versus 495 μg · hour/ml for 25 cases without adverse events; p = 0.98, one-tailed *t* test). A Grade 4 adverse event with elevated alanine aminotransferase of 358 possibly associated with study treatment did develop in one patient receiving 1,200 mg of rifapentine. The study treatment in this case was suspended, although the abnormal liver function was possibly attributed to excess alcohol use. Afterward the patient

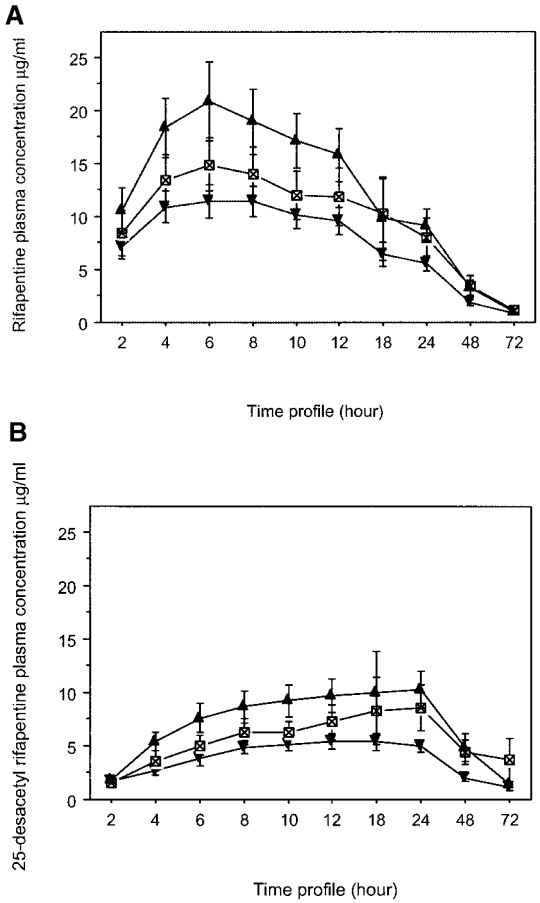

Figure 1. Mean rifapentine (*A*) and 25-desacetyl rifapentine (*B*) plasma concentrations versus time (hours) in patients with tuberculosis resulting from an oral dose of 600 mg (*inverted triangles*), 900 mg (*boxed crosses*), or 1,200 mg (*triangles*) of rifapentine obtained during once-weekly continuation phase tuberculosis therapy (n = 35 pharmacokinetic sessions; *error bars* = SE).

was successfully rechallenged with study drugs (rifapentine dose of 1,200 mg, and isoniazid) and completed study therapy. The rifapentine $AUC_{0-\infty}$ in this case was unexpectedly low for the rifapentine dose (rifapentine $AUC_{0-\infty}$ of 161 µg · hour/ml versus mean [95% confidence interval] of 477 [332–685] µg · hour/ml for all 13 patients administered rifapentine at 1,200 mg; and isoniazid AUC_{0-12} of 47 µg · hour/ml versus mean of 49 µg · hour/ml for all 35 patients). Elevated liver function tests (Grade 2) occurred in another patient treated with 600 mg of rifapentine after accidental overdosing of isoniazid with daily therapy (non-study regimen). However, the pharmacokinetic drug exposures with the correct drug regimen were unremarkable (rifapentine $AUC_{0-\infty}$ of 242 µg · hour/ml versus mean [95% confidence interval] of 296 [234–374] µg · hour/ml for 15 patients administered rifapentine at 600 mg; and isoniazid $AUC_{0-\infty}$ of 34 versus mean of 49 µg · hour/ml for all patients). The nine remaining reported adverse events were not related to study drugs.

Models to adjust for the effect of protein binding were constructed with estimates of active, free rifapentine and of free desacetyl rifapentine concentrations divided by the minimum inhibitory concentration of each drug for *M. tuberculosis*. The free rifapentine-to-MIC ratios and the combination ratio of free rifapentine plus desacetyl rifapentine were superior with higher rifapentine doses (Figure 3).

DISCUSSION

This pharmacokinetic study demonstrated the expected increase in total plasma (unbound and protein-bound) concentrations of rifapentine and its 25-desacetyl metabolite with an increase in dose to 900 and 1,200 mg. A linear dose relationship was observed with rifapentine $AUC_{0-\infty}$ between 600- and 1,200-mg doses ($AUC_{0-\infty}$, $r = 0.44$), but the association was less robust compared with rifapentine doses between 150 and 600 mg (17) in healthy, male volunteers of ideal body weight ($AUC_{0-\infty}$, $r = 0.9$). In this study, among patients with tuberculosis, disproportionately smaller mean increases in $AUC_{0-\infty}$ and maximum concentration were observed with dose increases from 600 mg to 1,200 mg, in contrast to increases seen in healthy male subjects with doses between 150 and 600 mg (17).

Rifapentine concentrations were lower in this study compared with other studies in normal volunteers and the differences are likely accounted for in part by the increased absorption of rifapentine with food in the other studies (18), although the effect(s) of tuberculosis cannot be excluded. In this study, drug administration was performed in the fasting state. For rifapentine at 600 mg, mean $AUC_{0-\infty}$ was 81%, and Cmax was 50%, of that found among normal volunteers administered 600 mg of rifapentine after breakfast (17). However, the rifapentine pharmacokinetic area under the concentration–time curve in this study were similar to that in the prior TBTC Study 22 (19) of patients with pulmonary tuberculosis, in which pharmacokinetic sampling was individualized to copy the estimated food intake estimated with drug administration of the patients' tuberculosis continuation-phase treatment. For rifapentine at 600 mg, mean AUC_{0-24} in TBTC Study 25 was 184 (95% confidence interval, 145–233) µg · hour/ml versus 195 (95% confidence interval, 175–216) µg · hour/ml in TBTC Study 22 (19) ($p = 0.65$, unpaired *t* test). The lack of a significant difference in rifapentine AUC between these two studies suggests that rifapentine AUC obtained after drug administration while fasting may in general replicate the rifapentine AUCs obtained on field administration of tuberculosis therapy in North America, in which it would be difficult to assure that all doses of therapy would be given with food.

Rifapentine $AUC_{0-\infty}$ was significantly associated with dose, plasma albumin concentration, sex, and race by multivariate regression analyses. Because rifapentine is highly protein bound *in vivo*, the association with plasma albumin was expected. Reith and coworkers reported (14), *in vitro*, 92.5% binding of [^{14}C]rifapentine (10 µg/ml) to human serum albumin (45 mg/ml) and 15.1% binding to α-1 acid glycoprotein (0.7 mg/ml). In human sera, rifapentine binding to protein ranged from 97 to 99% and binding of the 25-desacetyl metabolite averaged 93%. Even after adjustment for weight, rifapentine $AUC_{0-\infty}$ was significantly lower among men. Previously, among 351 patients with tuberculosis who received 600 mg of rifapentine, the apparent oral clearance of rifapentine for males and females was estimated as 2.51 ± 0.14 and 1.69 ± 0.41 L/hour, respectively (3). The explanation for this difference with sex is unknown.

No previous studies have examined the effect of race on rifapentine pharmacokinetics. The association between lower rifapentine $AUC_{0-\infty}$ and white race (composite of non-Hispanic and Hispanic) is of interest in this study, because in TBTC Study 22 (4, 19), non-Hispanic white race was independently associated with treatment failure/relapse in patients treated with once-weekly rifapentine and isoniazid (hazard ratio, 2.84; 95% confidence interval, 1.13–7.17; $p = 0.03$). However, in the same study, rifapentine AUC_{0-24} and Cmax were not significantly associated with treatment outcome ($p > 0.3$). Furthermore, white race was also a risk factor for failure/relapse among patients treated with

TABLE 2. RIFAPENTINE AND DESACETYL RIFAPENTINE PHARMACOKINETIC PARAMETERS OBTAINED AFTER ORAL DOSE OF RIFAPENTINE AT 600, 900, OR 1,200 MILLIGRAMS DURING ONCE-WEEKLY TUBERCULOSIS THERAPY

	Rifapentine Dose, Mean (*95% CI*)*			
	600 mg	900 mg	1,200 mg	p Value†
n	15	7	13	
Rifapentine				
$AUC_{0-\infty}$	296 (234–374)	410 (243–692)	477 (332–685)	0.02
Cmax	12.2 (9.6–15.5)	14.6 (9.5–22.6)	18.6 (13.1–26.3)	0.03
Half-life	14.4 (13.0–16.0)	16.4 (15.3–17.8)	14.4 (13.1–15.9)	0.90
Desacetyl rifapentine				
$AUC_{0-\infty}$	199 (165–287)	349 (281–536)	384 (258–659)	0.04
Cmax	5.9 (3.9–7.7)	6.7 (4.3–12.6)	10.9 (6.1–18.1)	0.02
Half-life	17.0 (15.0–22.1)	19.2 (16.1–22.5)	16.2 (14.3–20.6)	0.62

Definition of abbreviations: $AUC_{0-\infty}$ = mean area under the plasma concentration–time curve; CI = confidence interval; Cmax = mean rifapentine maximum concentration.

*Mean and 95% confidence interval were calculated from the natural log-transformed data and results were transformed back to original scale.

† p Value by regression analyses with comparison of natural log-transformed data with the three rifapentine doses.

twice-weekly rifampin and isoniazid (4), suggesting that the association between non-Hispanic white race and treatment outcome was not attributable simply to low total concentrations of rifapentine.

Significant interpatient variations in rifapentine concentration were noted in this study. Rifapentine metabolism by desacetylation is mediated by esterases and the heterogeneity in drug concentrations could be due in part to genetic polymorphisms involved in metabolism and disposition of drug (20, 21), as well as to differences in nutritional status, liver function, comorbidities, and severity of disease. No drug interaction with isoniazid was identified across the range of administered rifapentine doses.

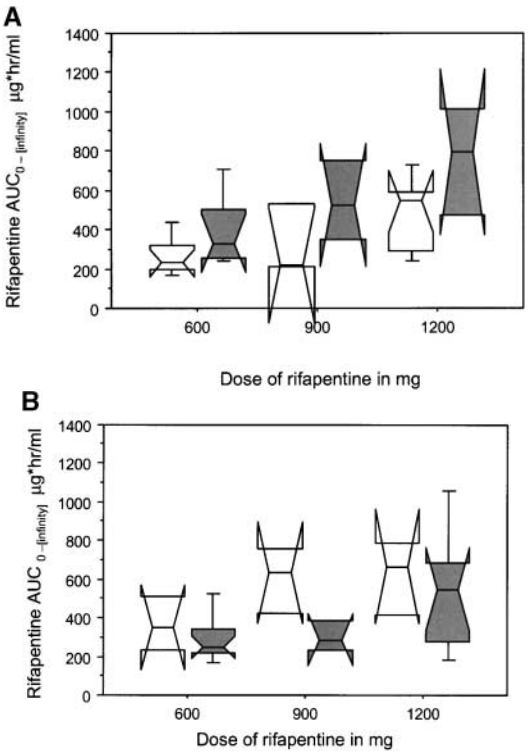

Figure 2. (*A*) Median rifapentine $AUC_{0-\infty}$ was lower in white individuals (*open boxes*) compared with nonwhite individuals (*shaded boxes*) at all doses (n = 35 pharmacokinetic sessions). (*B*) Also, median rifapentine $AUC_{0-\infty}$ was lower in males (*shaded boxes*) compared with females (*open boxes*) at all rifapentine doses (n = 35 pharmacokinetic sessions). The 25th and 75th percentiles are indicated by the bottom and top of each *box*, respectively; the 10th and 90th percentiles are indicated by *brackets*; and the 95% confidence intervals for the median are indicated by *notches*.

This pharmacokinetic substudy has several limitations. Patients enrolled into the pharmacokinetic substudy were more likely to have positive cultures for tuberculosis after 2 months of initial therapy and this slower response to treatment may have indicated more extensive disease when compared with other patients in TBTC Study 25. Rifapentine pharmacokinetics in this group are of considerable interest as patients with culture positivity at 2 months were more likely to fail/relapse with isoniazid and rifapentine, 600 mg once-weekly treatment, compared with standard therapy in a prior randomized trial (1, 4). However, markers of disease severity–including 2-month culture positivity, cavitary lung disease, body mass index, weight, and duration of study treatment before pharmacokinetic sampling, when adjusted for rifapentine dose in multivariate analyses, did not show associations with rifapentine area under the concentration–time curve or peak concentration. The small sample size, however, is a limitation regarding the definitiveness of conclusions reached by multivariate analysis. Also, fewer Asians and more Hispanics participated in the substudy compared with other subjects in TBTC Study 25, but because of the small study size, the primary analysis of race/ethnicity was simplified to compare white individuals (Hispanics and non-Hispanics) with others. The limitation of small sample size did not permit differences between races/ethnicities to be further differentiated.

All doses of rifapentine evaluated would superficially appear to be promising for therapy, maintaining total (protein-bound and free, active) concentrations in 34 of the 35 patients well above the MIC for rifapentine-susceptible *M. tuberculosis* (MIC of 0.05 μg/ml) for greater than 48 hours (Figure 1A). However, once-weekly rifapentine–isoniazid therapy with the 600-mg rifapentine dose was significantly less effective than twice- or thrice-weekly rifampin and isoniazid. An explanation of this inconsistency may be the high degree of protein binding of rifapentine and desacetyl rifapentine. The lack of association between treatment outcome and rifapentine drug area under the concentration–time curve in TBTC Study 22 was demonstrated only for total plasma (both protein-bound and free) rifapentine concentrations (19). Active, unbound plasma rifapentine concentrations were not measured. In models to adjust for the effect of protein binding, the time of active, free rifapentine and of free rifapentine plus desacetyl

TABLE 3. UNIVARIATE ANALYSIS OF AREA UNDER CONCENTRATION–TIME CURVE FOR RIFAPENTINE AND 25-DESACETYL METABOLITE: DEMOGRAPHIC, CLINICAL, AND LABORATORY AND RADIOGRAPHIC FACTORS

	Rifapentine $AUC_{0-\infty}$		25-Desacetyl Rifapentine $AUC_{0-\infty}$	
Independent Variable	Mean (*95% CI*)	p Value†	Mean (*95% CI*)	p Value†
Rifapentine therapy				
Rifapentine dose*				
Days on treatment: > 96 d (median)	434 (337–558)	0.13	364 (263–505)	0.07
Days on treatment: ⩽ 96 d (median)	325 (242–437)		237 (167–337)	
Demographic				
Age, > 44 yr (median)	365 (275–485)	0.75	300 (212–425)	0.95
Age, ⩽ 44 yr (median)	389 (293–515)		295 (206–424)	
Alcohol: Any consumption	383 (294–498)	0.89	318 (245–413)	0.62
Alcohol: No consumption	373 (278–501)		282 (190–420)	
Sex: Male	339 (268–429)	0.11	263 (199–347)	0.13
Sex: Female	463 (331–648)		386 (238–625)	
Illicit injection drug history present	335 (131–859)	0.65	263 (80–861)	0.75
Illicit injection drug history denied	383 (312–470)		301 (233–390)	
Race: White	329 (262–414)	0.11	256 (198–330)	0.12
Race: Nonwhite	452 (326–628)		369 (230–592)	
Clinical findings				
BMI > 22.65 (median)	442 (358–545)	0.10	376 (296–477)	0.04
BMI ⩽ 22.65 (median)	325 (237–446)		236 (156–355)	
Weight at PK study > 65.3 kg (median)	357 (283–452)	0.58	288 (218–381)	0.80
Weight at PK study ⩽ 65.3 kg (median)	397 (289–545)		306 (204–459)	
Laboratory and radiographic findings				
Albumin > 3.5 (median)	416 (321–540)	0.31	331 (233–472)	0.40
Albumin ⩽ 3.5 (median)	344 (256–461)		270 (190–384)	
ALT > 22 (median)	410 (327–515)	0.36	317 (325–427)	0.60
ALT ⩽ 22 (median)	345 (248–480)		280 (187–419)	
Bilateral infiltrates on X-ray	413 (307–556)	0.40	324 (241–437)	0.52
Bilateral infiltrates not on X-ray	351 (265–466)		280 (195–403)	
Lung cavity on X-ray at baseline or at 2 mo of therapy	346 (257–465)	0.38	234 (168–328)	0.08
No lung cavity on X-ray at baseline or at 2 mo of therapy	414 (307–559)		365 (249–534)	
MTB culture (+) at 2 mo of treatment	352 (245–507)	0.61	234 (155–354)	0.16
MTB culture (−) at 2 mo of treatment	391 (308–496)		334 (247–451)	

Definition of abbreviations: ALT = alanine aminotransferase; $AUC_{0-\infty}$ = mean area under the plasma concentration–time curve; BMI = body mass index; CI = confidence interval; MTB = *Mycobacterium tuberculosis*; PK = pharmacokinetic.

* *See* Table 2.

† Univariate analyses of differences in rifapentine $AUC_{0-\infty}$ between groups expressed as mean (95% CI) with p value by *t* test. Continuous independent variable(s) converted to dichotomous nominal factor(s) by division at median. Rifapentine $AUC_{0-\infty}$ was natural log transformed for mean (95% CI) and back transformed to original scale. The race variable compared white individuals (non-Hispanic and Hispanic) with others.

TABLE 4. MULTIVARIATE MODELS OF AREA UNDER CONCENTRATION–TIME CURVE FOR RIFAPENTINE AND 25-DESACETYL METABOLITE: DEMOGRAPHIC, CLINICAL, LABORATORY, AND TREATMENT FACTORS

	Rifapentine $AUC_{0-\infty}$ ($r^2 = 0.45$; $p = 0.001$)*			25-Desacetyl Rifapentine $AUC_{0-\infty}$ ($r^2 = 0.50$; $p = 0.0003$)*		
	Standardized Regression Coefficient	Regression Coefficient (*95% CI*)	p Value†	Standardized Regression Coefficient	Regression Coefficient (*95% CI*)	p Value†
Rifapentine dose, g	0.49	0.99 (0.41–1.57)	0.002	0.53	1.35 (0.64–2.06)	0.0006
Nonwhite race	0.38	0.42 (0.11–0.73)	0.01	0.43	0.59 (0.21–0.97)	0.004
Female sex	0.32	0.37 (0.05–0.69)	0.03	0.40	0.57 (0.18–0.97)	0.006
Albumin concentration	0.29	0.32 (0.01–0.63)	0.04	0.39	0.53 (0.16–0.91)	0.007

Definition of abbreviations: $AUC_{0-\infty}$ = mean area under the plasma concentration–time curve; CI = confidence interval.

* Multivariate models of rifapentine $AUC_{0-\infty}$ and 25-desacetyl rifapentine $AUC_{0-\infty}$ by stepwise regression are presented. Independent demographic, clinical, and laboratory variables from Tables 2 and 3 (*see* Methods) were entered into the model, using continuous variables when available (not dichotomized); for the final model, rifapentine dose and albumin concentrations were continuous, and sex and race were categorical. The race variable compared white individuals (non-Hispanic and Hispanic) with others.

† p Values were adjusted for all other effects in the final model.

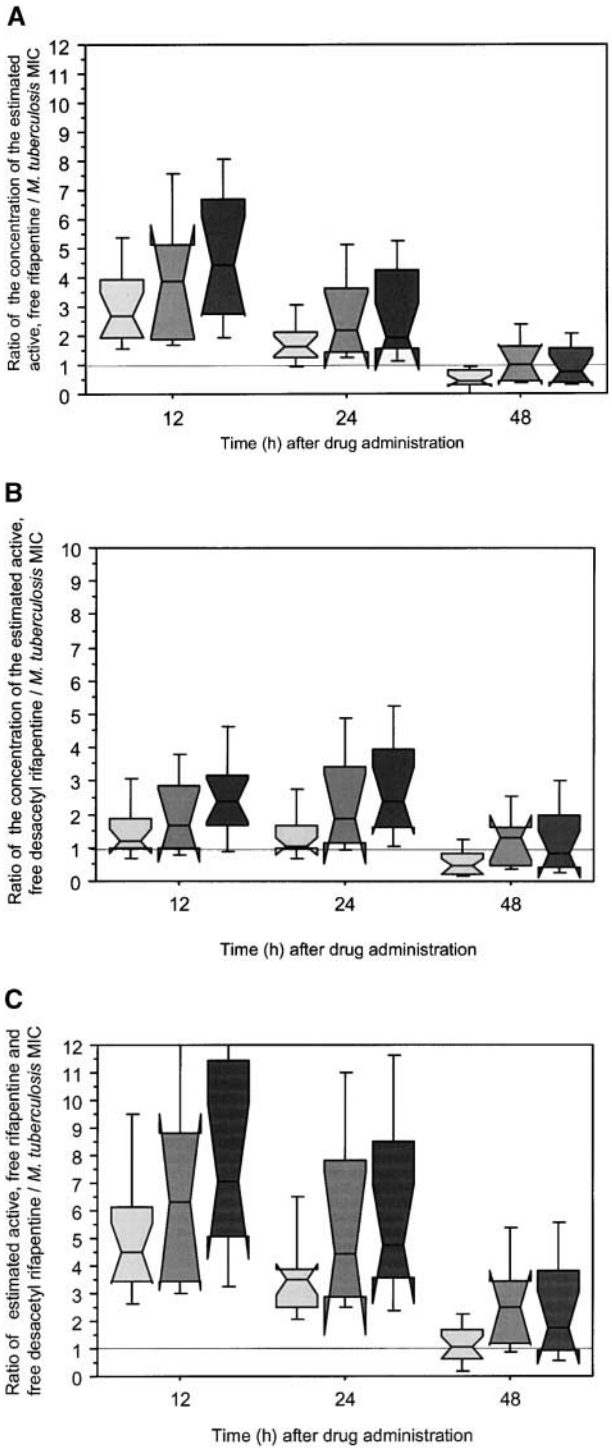

Figure 3. (*A*) The ratio of estimated plasma concentration of active, free rifapentine divided by the minimum inhibitory concentration (MIC) of *M. tuberculosis* is plotted versus time in *box plots* with median ratios shown for rifapentine at doses of 600 (*light-shaded boxes*), 900 (*medium-shaded boxes*), and 1,200 mg (*dark-shaded boxes*). The 25th and 75th percentiles are indicated by the bottom and top of each *box,* respectively; the 10th and 90th percentiles are indicated by *brackets;* and the 95% confidence intervals for the median are indicated by *notches.* Similar ratios were calculated for active, free desacetyl rifapentine divided by the MIC of *M. tuberculosis* (*B*) and for the estimated total activity of free, unbound rifapentine plus desacetyl rifapentine divided by the *M. tuberculosis* MIC (*C*). The ratios of active, free rifapentine, desacetyl metabolite and the combination of rifapentine and the desacetyl metabolite divided by MIC were superior (greater than 1) with higher rifapentine doses.

rifapentine concentration over the minimum inhibitory concentration in plasma (ratio of free drug to MIC, greater than 1) were estimated to be superior with rifapentine doses greater than 600 mg (Figure 3), although considerable exposure to subtherapeutic rifapentine concentrations might also be anticipated (time with ratio of detectable free drug to MIC, less than 1).

Another factor complicating dose selection of rifapentine concerns a number of uncertainties about the pharmacodynamics of the entire rifamycin class. Intracellular penetration and activity may be important in the process of sterilizing tuberculous lesions, and there are conflicting data regarding the intracellular activity of rifapentine (22, 23). Finally, our study illustrates the pharmacokinetic mismatch between rifapentine and isoniazid; 54% of patients had rifapentine and desacetyl rifapentine concentrations detected for more than 36 hours after clearance of concurrently administered isoniazid. Prolonged exposure to rifapentine in the absence of isoniazid may explain, in part, the occurrence of acquired rifamycin resistance among patients with HIV-related tuberculosis treated with once-weekly rifapentine plus isoniazid (5).

Dosing with rifapentine is not currently based on weight, in contrast to other antituberculosis drugs. In a rifapentine tolerability trial (9), there was a trend ($p = 0.06$) toward higher study drug-related toxicity at doses greater than 20 mg/kg. In the current pharmacokinetic substudy, however, there was no association between greater rifapentine $AUC_{0-\infty}$ and adverse events reported for any cause. However, only 3 of 35 patients received a rifapentine dose greater than 20 mg/kg. Additional experience is needed to better evaluate potential toxicity associated with rifapentine and to determine a clinically optimal rifapentine treatment dose.

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