Clinical Evaluation of the Nelfinavir-Rifabutin Interaction in Patients with Tuberculosis and Human Immunodeficiency Virus Infection

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Study Objective. To characterize the bidirectional interaction between twice-daily nelfinavir and twice-weekly rifabutin and isoniazid in patients with tuberculosis and human immunodeficiency virus (HIV) infection.

Design. Prospective cohort study.

Setting. Three clinical research centers.

Patients. Seven patients with HIV-related tuberculosis.

Intervention. Rifabutin 300 mg and isoniazid 15 mg/kg (maximum dose 900 mg) twice/week were administered for at least 2 weeks during the continuation phase of tuberculosis treatment. Antiretroviral therapy with nelfinavir 1250 mg twice/day and two nucleoside reverse transcriptase inhibitors was then added.

Measurements and Main Results. Patients underwent blood sampling for pharmacokinetic analysis during the continuation phase of tuberculosis therapy and after a median of 21 days after the addition of antiretroviral treatment. When rifabutin was coadministered with nelfinavir, its area under the concentration-time curve from 0–21 hours ($AUC_{0–21}$) increased 22% (geometric mean 5.01 µg•hr/ml [90% confidence interval (CI) 3.25–7.71] with nelfinavir vs 4.10 µg•hr/ml [90% CI 3.18–5.27] without nelfinavir; geometric mean ratio 1.22 [90% CI 0.78–1.92]). Also, the $AUC_{0–21}$ for the active metabolite, desacetylrifabutin, increased significantly (geometric mean ratio 3.46, 90% CI 1.84–6.47, p=0.009). In the presence of rifabutin, the pharmacokinetic parameters of nelfinavir and its principal metabolite M8 were similar to those of patients not taking rifabutin. No drug interaction between nelfinavir and isoniazid was detected.

Conclusions. Coadministration of rifabutin and isoniazid without dosage adjustment during twice-weekly tuberculosis therapy with nelfinavir-based antiretroviral therapy resulted in rifabutin exposures within the acceptable ranges for safety and efficacy. Therefore, this combination is an appropriate option for the simultaneous treatment of tuberculosis and HIV infection when tuberculosis therapy is given twice weekly.

Key Words: tuberculosis, human immunodeficiency virus, HIV, nelfinavir, rifabutin, isoniazid, drug interactions, cytochrome P450, pharmacokinetics.

(Pharmacotherapy 2007;27(6):793–800)

Rifamycins are the key drugs in the treatment of active disease due to *Mycobacterium tuberculosis* because they allow for a short course of tuberculosis therapy and because they reduce

morbidity and mortality due to human immunodeficiency virus (HIV)–related tuberculosis.[1, 2] However, rifampin is a potent inducer of hepatic microsomal enzymes, and it substantially reduces concentrations of most HIV type 1 protease inhibitors. Therefore, rifabutin, which is only about 40% as potent an inducer as rifampin, is recommended for patients who are taking an antiretroviral regimen with a protease inhibitor, including nelfinavir.[2] Despite this, rifabutin can substantially reduce the plasma concentrations of nelfinavir.

Cytochrome P450 (CYP) 3A4 partly clears rifabutin, unlike rifampin, and this isoenzyme predominantly clears the active 25-desacetyl-metabolite. Therefore, also unlike rifampin, rifabutin is subject to bidirectional drug interactions.[3] Nelfinavir is a potent inhibitor of CYP3A4 and, therefore, might increase exposure to rifabutin and desacetylrifabutin. Elevated concentrations of rifabutin and its metabolite are associated with an increased frequency of adverse drug reactions, including anterior uveitis and thrombocytopenia.[4]

In healthy volunteers, rifabutin 150 mg/day did not substantially affect the pharmacokinetics of nelfinavir 1250 twice/day.[5] However, the area under the concentration-time curve (AUC) for rifabutin increased by 71% compared with rifabutin 300 mg dosed alone. The effect on the 25-*O*-desacetyl metabolite was dramatic, with a 11.2-fold increase in the AUC.

Although nelfinavir is no longer part of the preferred regimens to treat HIV infection, it remains an alternative for patients who cannot receive nonnucleoside reverse transcriptase inhibitors or ritonavir-boosted protease inhibitors.[6] During pregnancy, nelfinavir is a recommended protease inhibitor given the extensive pharmacokinetic and clinical experience with this drug in pregnant women and given the absence of evidence for teratogenicity.[7] Therefore, understanding the nelfinavir- rifabutin interaction remains relevant.

Rifamycins result in concentration-dependent mycobacterial killing. Therefore, low rifamycin concentrations are highly undesirable.[8, 9] Because of concerns about underdosing of rifabutin during intermittent therapy, current guidelines from the Centers for Disease Control and Prevention (CDC) recommend rifabutin 300 mg for twice-weekly tuberculosis therapy in patients with $CD4^+$ counts of 100 cells/mm^3 or greater who are receiving nelfinavir.[2] To evaluate this recommendation, we characterized the bidirectional pharmacokinetic interactions between nelfinavir and rifabutin in patients with HIV and tuberculosis coinfection. In addition, we determined pharmacokinetic parameters for isoniazid in the absence and presence of nelfinavir. Patients were also enrolled in the Tuberculosis Trials Consortium (TBTC)–U.S. Public Health Service Study 23, which was designed as an observational trial to evaluate the efficacy and tolerability of a standard rifabutin-based regimen to treat HIV-related tuberculosis.[10]

Methods

Patients

The institutional review boards of the CDC and the three participating sites approved this study. Patients with HIV-related tuberculosis were eligible for inclusion; all patients provided written informed consent.

Exclusion criteria were severe anemia (hematocrit < 25%), pregnancy or breastfeeding, consumption of grapefruit juice, use of a nonnucleoside reverse transcriptase inhibitor, use of a second protease inhibitor, or use of any drug specifically contraindicated to nelfinavir or rifabutin or with the potential to alter concentrations of these drugs within the 5 days before or during periods of pharmacokinetic monitoring.

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Supported by the Centers for Disease Control and Prevention, the U.S. Public Health Service, and Pfizer Inc. Bayer Diagnostics provided test kits to assess human immunodeficiency viral load. The Frederic C. Bartter General Clinical Research Center at the Veterans Affairs Medical Center San Antonio supported by a National Institutes of Health grant (MO1-RR-01346) provided assistance in the evaluation of some patients.

Presented in part at the international conference of the American Thoracic Society, Orlando, Florida, May 21–26, 2004.

Manuscript received August 30, 2006. Accepted pending revisions November 3, 2006. Accepted for publication in final form January 31, 2007.

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Sample and Data Collection

Initial pharmacokinetic sampling occurred after rifabutin 300 mg and isoniazid 15 mg/kg (maximum dose 900 mg) were administered twice/week for at least 2 weeks during the continuation phase of tuberculosis treatment (months 3–6). Antiretroviral treatment with nelfinavir 1250 mg twice/day (given as five 250-mg tablets) and two nucleoside reverse transcriptase inhibitors was then added. The nucleoside reverse transcriptase inhibitors were zidovudine, lamivudine, stavudine, or didanosine in combinations suggested in guidelines from the U.S. Department of Health and Human Services.[6]

After a median of 21 days (interquartile range 20–38 days), a second set of pharmacokinetic samples was obtained. Blood samples for analyses were collected just before the observed doses and 1, 3, 5, 7, 9, and 21 hours after rifabutin and isoniazid were administered. These times corresponded to 2, 4, 6, 8, 10, 12, and 24 hours after nelfinavir was given. Patients took rifabutin and isoniazid while fasting for 2 hours before and 1 hour after drug administration, and they took nelfinavir with a meal containing 22–32% fat.

All administered doses of tuberculosis therapy were directly observed. Sixty days after the last dose of the study drugs was given, all patients were interviewed by phone or in person, and their medical records were reviewed for evidence of adverse events.

Drug Analyses

Concentrations of nelfinavir and hydroxy-*t*-butylamide (M8, the active metabolite of nelfinavir) were compared with those of 10 HIV-infected patients receiving nelfinavir 1250 mg twice/day for 28 days without rifabutin.[11]

Validated high-performance liquid chromatographic assays were used to determine concentrations of isoniazid,[12] rifabutin, and the 25-desacetyl metabolite of rifabutin. Assays were performed at the National Jewish Medical and Research Center in Denver, Colorado. Samples were measured by using a system consisting of a pump with a fixed-volume autosampler, and an ultraviolet detector (models P4000 HPLC, AS1000, UV2000, respectively; ThermoFinnegan, San Jose, CA), a computer (e series; Gateway, Inc., Irvine, CA), and a high-performance liquid chromatographic data-management system (ChromQuest; Thermo Fisher Scientific, Inc. Waltham, MA).

The plasma standard curve for isoniazid ranged from 0.5–20 µg/ml. The absolute recovery of isoniazid from plasma was 61%. The within-sample precision (percentage coefficient of variation) of validation quality control samples was 1–6%, and the overall validation precision across all standards was 6–10%.

The plasma standard curve for rifabutin ranged from 0.01–2 µg/ml. The absolute recovery of rifabutin from plasma was 100%. The within-sample precision (percentage coefficient of variation) of validation quality control samples was 3–4%, and the overall validation precision across all standards was 2–7%.

We observed no interference in the measurement of isoniazid or rifabutin with 90 commonly used drugs. Plasma drug concentrations of nelfinavir and its metabolite M8 were determined at PPD, Inc., Wilmington, NC, as previously reported.[13, 14] Assays for HIV loads (Versant HIV-1 RNA 3.0 assay [bDNA]; Bayer Diagnostics, Emeryville, CA) were conducted in the laboratory of Dr. Howard Gale at the Veterans Affairs Medical Center, Washington, D.C.

Statistical and Pharmacokinetic Analyses

Drug exposure was defined as the AUC from 0–21 hours ($AUC_{0–21}$) for rifabutin and from 0–12 hours ($AUC_{0–12}$) for nelfinavir and isoniazid. These AUCs were analyzed by using noncompartmental techniques (WinNonlin, version 4; Pharsight Corp., Mountain View, CA). Because rifabutin has an extended terminal elimination phase[3] and because accurate calculations of half-life were not possible with our 21-hour sampling scheme, its half-life was not reported.

Because twice-weekly regimens are no longer recommended for HIV-positive patients with tuberculosis and a $CD4^+$ count below 100 cells/mm^3,[15] we performed simulations of rifabutin 300 mg 3 times/week using WinNonlin. Nonparametric superposition was performed by using all of the available serum concentration data for rifabutin in the presence of nelfinavir simulated over 2 weeks.

Data analyses were performed by using SAS statistical software (SAS Institute Inc., Cary, NC). For binomial data, differences between groups were determined by using a χ^2 or Fisher exact test. Pharmacokinetic data were reported as arithmetic and geometric means with 90% confidence intervals (CIs), and paired data were compared by applying the *t* test. If a normal distribution was rejected on the basis of a

Shapiro-Wilk test or if variances of different groups were unequal and natural-log transformation improved the validity of the analyses, the *t* test was performed with natural log–transformed results. These natural log–transformed data were then back-transformed to the original scale to obtain the mean and 90% CI. Differences between groups were considered statistically significant if the p value was less than 0.05.

Results

Eight patients were enrolled in the study; one patient was excluded from the analysis because fluconazole was administered during pharmacokinetic sampling. Pharmacokinetics for isoniazid were omitted from another patient whose isoniazid concentrations were not detected after 1-hour sampling. Table 1 shows the demographic and laboratory data of the seven evaluable patients. Because nucleoside reverse transcriptase inhibitors are not known to interact with isoniazid or rifabutin, interactions described here were attributed to nelfinavir. Concentrations of rifabutin were somewhat higher in the presence of nelfinavir than in its absence. The geometric mean $AUC_{0–21}$ for rifabutin was 5.01 µg•hr/ml (90% CI 3.25–7.71) versus 4.10 µg•hr/ml (90% CI 3.18–5.27), and the geometric mean ratio was 1.22 (90% CI, 0.78–1.92) (Table 2, Figure 1). A significant interaction could not be excluded given the sample size.

If we were to conduct a post hoc analysis of the data using a 1-sample *t* test of the differences between paired observations and assuming a normal distribution, a sample of 18 would have been necessary to achieve 79% power with an α of 0.05 to detect a difference of 1.318 µg•hour/ml between the baseline mean $AUC_{0–21}$ of 4.295 µg•hour/ml for rifabutin and a second mean of 5.613 µg•hour/ml with a known standard deviation of 2.356.

The $AUC_{0–21}$ for the 25-desacetyl metabolite of rifabutin was significantly higher with nelfinavir coadministration than at baseline without nelfinavir (Table 2, Figure 1). Simulations of rifabutin 300 mg 3 times/week in the presence of nelfinavir for 2 weeks showed a median maximum concentration of 0.43 µg/ml, a 21-hour value of 0.12 mg/ml, and an $AUC_{0–21}$ of 5.41 µg•hour/ml for rifabutin.

Nelfinavir did not significantly affect serum concentrations of isoniazid (Table 2). In the presence of rifabutin, concentrations of nelfinavir and M8 were similar to those of HIV-infected patients receiving nelfinavir without rifabutin (Table 3).[11] Median $CD4^+$ T-cell counts rose from 94 cells/mm^3 (interquartile range 59–145 cells/mm^3) at baseline to 198 cells/mm^3 (interquartile range 112–438 cells/mm^3) during antiretroviral therapy, and HIV RNA content decreased from 5.40 $\log_{10}$ copies/ml (interquartile range 5.03–5.70 copies/ml) to 2.84 $\log_{10}$ copies/ml (interquartile range 2.19–3.21 copies/ml, p=0.02) at a median of 21 (interquartile range 20–38) days after the start of antiretroviral therapy.

All seven patients successfully completed tuberculosis therapy. No patient experienced tuberculosis treatment failure or had a relapse.

Table 1. Demographic and Laboratory Data for the Seven Patients

Variable	Value
	No. (%) of Patients
Race/ethnicity	
Caucasian or Hispanic	6 (86)
African-American	1 (14)
Sex	
Male	6 (86)
Female	1 (14)
Hepatitis B surface antigen–positive	0
Hepatitis C serology–positive	1 (14)
	Median (interquartile range)
Body mass index (kg/m^2)	20.99 (20.25–24.47)
Karnofsky score[a]	80 (80–90)
$CD4^+$ cell count[b]	94 (52–159)
HIV-RNA viral load ($\log_{10}$)[b]	5.44 (5.03–5.70)
Aspartate aminotransferase level (U/L)[b]	50 (38–74)
Bilirubin level (mg/dl)[b]	0.3 (0.2–0.4)
Albumin level (g/dl)[b]	3.3 (3.2–3.6)
Prothrombin time (sec)	12 (11–12)

[a]The Karnofsky score measures functional performance (activities of daily living). On a scale of 0–100, lower scores indicate worse chances of survival for most serious illnesses.
[b]From first pharmacokinetic sample.

Toxicity

Two patients developed toxicity that was possibly attributable to tuberculosis therapy combined with antiretroviral therapy. In the first patient, aspartate aminotransferase (AST) levels were elevated (range 61–171 U/L) before antiretroviral therapy. This patient developed grade III transaminase elevations (AST level 197 U/L) 14 days after the addition of zidovudine, lamivudine, and nelfinavir to isoniazid and rifabutin 300 mg twice/week. Marked increases were observed in the patient's exposure to rifabutin ($AUC_{0–21}$ change from 5.3 to 8.7

Table 2. Comparison of Rifabutin, Desacetylrifabutin, and Isoniazid Pharmacokinetic Parameters for Rifabutin 300 mg and Isoniazid Administered With and Without Nelfinavir-Based Antiretroviral Therapy[a]

Parameter	Geometric Mean (90% CI) Rifabutin + Isoniazid With Nelfinavir	Rifabutin + Isoniazid Without Nelfinavir	Geometric Mean Ratio (with:without nelfinavir)	p Value
Rifabutin (n=7)				
AUC_{0-21} (µg•hr/ml)	5.01 (3.25–7.71)	4.10 (3.18–5.27)	1.22 (0.78–1.92)	0.42
C_{max} (µg/ml)	0.42 (0.24–0.75)	0.43 (0.34–0.56)	0.97 (0.54–1.75)	0.60
25-Desacetylrifabutin (n=7)				
AUC_{0-21} (µg•hr/ml)	1.96 (1.26–3.04)	0.57 (0.31–1.02)	3.46 (1.84–6.47)	0.009
C_{max} (µg/ml)	0.14 (0.08–0.23)	0.06 (0.04–0.09)	2.42 (1.41–4.15)	0.02
Isoniazid (n=6)				
AUC_{0-12} (µg•hr/ml)	23.9 (16.2–35.2)	22.8 (15.3–34.0)	1.05 (0.81–1.36)	0.72
C_{max} (µg/ml)	7.96 (5.55–11.42)	6.15 (4.30–8.78)	1.30 (0.80–2.09)	0.33
Half-life (hrs)	1.43 (0.84–2.46)	1.83 (1.07–3.13)		0.14

CI = confidence interval; AUC_{0-12} = area under the concentration-time curve from 0–21 hours; C_{max} = maximum concentration.
[a]Nucleoside reverse transcriptase inhibitors were zidovudine, lamivudine, stavudine, or didanosine in combinations suggested by U.S.P.H.S. guidelines.[6]

µg•hr/ml) and desacetylrifabutin (AUC_{0-21} change from 0.8 to 4.0 µg•hr/ml) in the presence of nelfinavir. Nelfinavir exposures were close to the median. Therapy was withheld for 6 days and resumed at the same dosing as before without further difficulty. The follow-up AST concentration during tuberculosis and antiretroviral therapy was 145 U/L.

The second patient developed grade IV neutropenia (absolute neutrophil count of 394.4 cells/mm^3) 2 months after the addition of stavudine, lamivudine, and nelfinavir to isoniazid and rifabutin 300 mg twice/week. Rifabutin exposures changed only modestly (AUC_{0-21} change from 6.0 to 6.8 µg•hr/ml, desacetylrifabutin change from 1.5 to 1.8 µg•hr/ml). Tuberculosis and HIV therapy, including trimethoprim-sulfamethoxazole prophylaxis, were not interrupted. Repeat absolute neutrophil counts remained below 600 cells/mm^3 6 weeks after the completion of tuberculosis treatment.

Discussion

Our results suggested that the concentrations of rifabutin were adequate and reasonably well tolerated when rifabutin 300 mg was coadministered twice weekly with nelfinavir 1250 twice/day. A formal therapeutic window has not been defined for rifabutin in the treatment of tuberculosis. However, in one study, below-normal plasma concentrations were associated with treatment failure or relapse and with

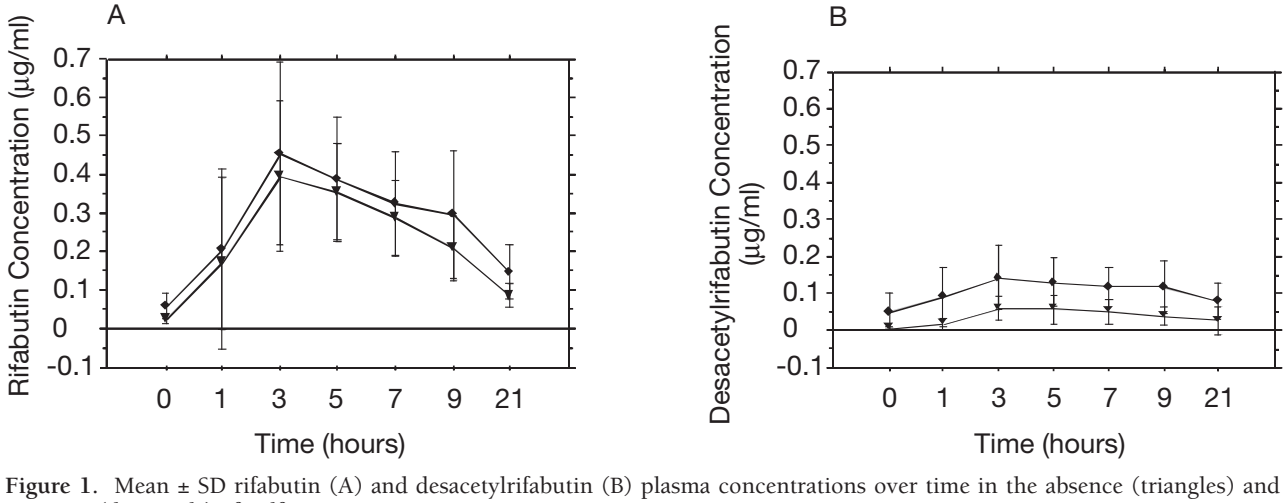

Figure 1. Mean ± SD rifabutin (A) and desacetylrifabutin (B) plasma concentrations over time in the absence (triangles) and presence (diamonds) of nelfinavir.

Table 3. Comparison of Nelfinavir and M8 Metabolite Pharmacokinetic Parameters in the Presence and Absence of Rifabutin

Parameter	Nelfinavir	p Value	M8 Metabolite	p Value
AUC_{0-12} (µg•hr/ml)		0.81		0.31
With rifabutin	28.33 ± 9.87		8.73 ± 5.33	
Without rifabutin	26.4 ± 7.9		11.9 ± 5.5	
C_{max} (µg/ml)		0.97		0.84
With rifabutin	3.93 ± 1.08		1.50 ± 0.84	
Without rifabutin	3.99 ± 0.78		1.85 ± 0.60	
C_{min} (µg/ml)[a]		0.69		0.06
With rifabutin	0.70 ± 0.74		0.15 ± 0.12	
Without rifabutin	0.69 ± 0.42		0.30 ± 0.23	

Data are arithmetic mean ± SD.
[a]Measured in the afternoon or evening.

acquired rifamycin resistance among patients with HIV infection and tuberculosis who receive twice-weekly tuberculosis therapy.[16] In those patients, the AUC_{0-24} for rifabutin was less than 4.5 µg•hour/ml in five (83%) of six patients with acquired rifamycin-resistant treatment failure or relapse. All had advanced acquired immunodeficiency syndrome with $CD4^+$ counts of less 100 cells/mm^3 compared with 33 (35%) of 94 subjects without acquired rifamycin resistance (p=0.03, Fisher exact test). In our study, the AUC_{0-21} for rifabutin was greater than 4.5 µg•hour/ml in six (86%) of seven patients receiving rifabutin and nelfinavir-based antiretroviral therapy, whereas three (43%) of seven had rifabutin concentrations greater than this threshold in the absence of nelfinavir.

The AUC for the desacetylrifabutin metabolite is normally about 10% that of the parent compound, with similar antimycobacterial activity.[17–19] However, its contribution to toxicity is not well understood. Whereas CYP3A4 only partially metabolizes rifabutin, it predominantly metabolizes desacetyl metabolite; therefore, CYP3A inhibition increases levels of this metabolite more than it raises levels of rifabutin. At baseline, the mean AUC_{0-21} for desacetylrifabutin was 14% of the AUC_{0-21} for rifabutin. However, with nelfinavir-induced inhibition of CYP450, desacetylrifabutin exposure increased 3.5-fold and was 39% of the AUC_{0-21} for rifabutin. One patient who developed hepatotoxicity after the addition of antiretroviral therapy had the highest concentrations of both rifabutin and the desacetyl metabolite in this study. However, preliminary evaluation of toxicity data from the pharmacokinetic substudy of the Tuberculosis Trials Consortium Study 23 did not reveal an association of neutropenia or hepatotoxicity with rifabutin exposure.[16, 20] Furthermore, available data suggest that rifamycin hepatotoxicity is idiosyncratic.[21]

The data confirm the provisional CDC guideline that dosage adjustment is unnecessary when rifabutin is administered twice weekly with nelfinavir-based antiretroviral therapy.[2] Compared with daily dosing of rifabutin, twice-weekly dosing had a reduced effect on steady-state exposures and, thus, may minimize the risk of thrombocytopenia, neutropenia, and uveitis. Although twice-weekly tuberculosis therapy is no longer recommended for patients with $CD4^+$ counts less than 100 cells/mm^3,[15] it remains an important option for directly observed therapy in patients with cell counts higher than this. Furthermore, the simulations of rifabutin 300 mg given 3 times/week in the presence of nelfinavir predicted rifabutin serum concentrations and AUC_{0-21} values within ranges that are likely to be safe and effective.

In the presence of rifabutin 300 mg and isoniazid administered twice weekly, concentrations of nelfinavir were similar to those achieved in historical patients infected with HIV who received nelfinavir without rifabutin.[11] This observation is consistent with findings from studies in which CYP inducers other than rifampin did not substantially affect concentrations of nelfinavir.[11, 22] Therapeutic trough nelfinavir concentrations (minimum concentrations > 0.8 µg/ml for wild-type HIV)[23, 24] were present in only three of our six patients. However, it is difficult to attribute this finding to the presence of rifabutin because similar findings were demonstrated in the absence of CYP inducers in the clinical setting.[25, 26] Of note, a new formulation of nelfinavir, a 625-mg tablet, is available. This formulation increases bioavail-

ability (24% increase in the AUC) compared with the 250-mg tablet used in this study.[11]

Hydroxy-*t*-butylamide (M8), the major oxidative metabolite of nelfinavir, has HIV activity comparable to that of the parent compound in vitro, and it may account for some of the clinical efficacy of nelfinavir.[27] The low minimum concentration of M8 in this study (0.15 ± 0.12 µg/ml) was not unexpected (minimum concentration in historical subjects 0.30 ± 0.23 µg/ml, p=0.06). Although transformation of nelfinavir to M8 appears to involve solely CYP2C19, CYP3A4 metabolizes M8, making it more susceptible than nelfinavir to induction by rifabutin.[28] However, low concentrations of M8 in the presence of CYP3A4 inducers do not substantially affect overall concentrations of nelfinavir plus M8, and they are not expected to be clinically significant.[27, 28]

This pharmacokinetic study had several important limitations. First, the small sample size limited the power of the findings. Second, we did not definitively establish or exclude a significant increase in the concentrations of rifabutin in the presence of nelfinavir, as the 90% CIs for the ratio of geometric means for rifabutin AUC were outside the equivalence range standard of 80–125%. Third, our 21-hour sampling scheme was insufficient to accurately determine some pharmacokinetic parameters, such as the half-life of rifabutin. Finally, the follow-up of 2 months beyond the last pharmacokinetic sampling was too short to enable us to evaluate the durability of nelfinavir-based antiretroviral therapy.

Conclusion

For patients with HIV infection and tuberculosis, standard dosing of twice-weekly rifabutin therapy with daily nelfinavir-based antiretroviral therapy achieved acceptable drug exposures of rifabutin. Our findings support current recommendations to provide rifabutin 150 mg for daily treatment but 300 mg for twice-weekly treatment. Further clinical studies are needed to identify optimally safe, potent, and durable antiretroviral therapies for patients with HIV infection who are receiving treatment for tuberculosis.

Acknowledgments

We are grateful to Drs. Elsa Villarino, Rick O'Brien, and Kenneth G. Castro for their support and leadership in the CDC.

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