The Clinical Pharmacokinetics of Rifabutin

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Rifabutin is structurally similar to rifampin, but there are important pharmacokinetic differences between the two drugs. Rifabutin is more lipid soluble than is rifampin, resulting in more-extensive tissue uptake, a larger volume of distribution, lower maximum plasma concentrations, lower trough concentrations, a longer terminal half-life, and higher tissue-to-plasma drug concentration ratios. The oral bioavailability of rifabutin is low. Like rifampin, rifabutin induces its own metabolism during multiple dosing. Rifabutin is extensively metabolized. The two major metabolites of rifabutin contribute to its antimicrobial activity. Rifabutin induces hepatic metabolism but is not as potent an inducer as is rifampin. Rifabutin does not affect the pharmacokinetics of antiretroviral drugs that are excreted in the urine. Although rifabutin decreases plasma concentrations of zidovudine, this finding does not appear to be clinically relevant. When administered during rifabutin prophylaxis, fluconazole decreases the incidence of *Mycobacterium avium* complex bacteremia. The coadministration of clarithromycin and rifabutin results in increased plasma concentrations of rifabutin and decreased plasma concentrations of clarithromycin; however, the plasma concentration of clarithromycin's active metabolite is increased.

There is a substantial overlap in the antimicrobial spectrums of rifabutin and rifampin; however, there are some important differences between these drugs, particularly in their antimycobacterial activity. Their respective pharmacokinetic profiles are profoundly different. The physicochemical property that contributes most to the pharmacokinetic divergence of these drugs is the difference in their lipid solubility (table 1). Other factors that distinguish the pharmacokinetics of rifabutin from those of rifampin include the antimicrobial activities of its two major metabolites, 25-O-desacetyl rifabutin (with activity almost equivalent to that of rifabutin) and 31-OH rifabutin (with a potency of ~10% that of rifabutin).

The pharmacokinetics and pharmacological activity of rifabutin are discussed as they relate to these physicochemical and metabolic properties.

Pharmacokinetic Profile of Rifabutin

Metabolism

The disposition of a single 270-mg dose of [^{14}C]rifabutin in healthy volunteers is shown in figure 1. Four hours after oral administration, 65%–88% of the drug in plasma is in the unchanged form. The concentration of the two major metabolites, 25-O-desacetyl rifabutin and 31-OH rifabutin, are ~5% and ~10%, respectively, that of the parent compound. The many other metabolites of rifabutin account for the substantial difference seen at later time points between the total radiolabel in plasma and the radiolabel accounted for by rifabutin and the major metabolites. At least four urinary metabolites of rifabutin have been identified: 32-OH rifabutin, 32-OH-25-O-desacetyl rifabutin, 25-O-desacetyl rifabutin *N*-oxide, and 32-OH-rifabutin [3].

Comparison of the Pharmacokinetics of Rifabutin and Rifampin

The maximum plasma concentration (C_{max}) of rifabutin is ~10-fold lower than that of rifampin, and the elimination half-life ($t_{1/2}$) is ~10-fold higher [1, 4]. However, the difference in oral clearance, expressed as systemic clearance (Cl_s) divided by the bioavailability (F), is more modest (table 1). Approximately 90%–95% of both drugs is eliminated by metabolic processes, with little of either drug eliminated unchanged in the urine [1, 3].

The large difference in the $t_{1/2}$ values of the two drugs is related primarily to the difference in their oil/water partition coefficients. Because of its high lipid solubility, rifabutin is extensively distributed in the tissues. The mean volume of distribution, as determined in five patients with HIV infection who were receiving rifabutin intravenously, was 9.3 L/kg [5]. The corresponding value for rifampin has been reported to be ~1 L/kg [1, 6]. The distribution of rifabutin is relatively slow and is apparent even with oral dosing, as shown in figure 1. The plasma concentration curves show a clear distribution phase or "nose," with a distribution $t_{1/2}$ of ~2–3 hours [5]. The long terminal $t_{1/2}$ of rifabutin allows for once-daily dosing.

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Table 1. Physicochemical and pharmacokinetic properties of rifampin and rifabutin.

Property	Rifampin [1]	Rifabutin [2]
Physicochemical		
Molecular weight	823	847
pK_a	1.7, 7.9	6.9
Oil/water partition coefficient	16	>100
Un-ionized fraction pH 7.4	Zwitterion	0.76
Pharmacokinetic		
C_{max} (ng/mL)	3,500 ng/mL	460 ng/mL
$t_{\frac{1}{2}}$ (h)*	3.5 ± 0.8	45 ± 16
Cl_s/F (L/h·kg)*	0.21 ± 0.10†	0.69 ± 0.32
V_{SS}/F (L/kg)*	0.97 ± 0.36†	45 ± 17‡
X_u (%)*	7 ± 3	6 ± 2

NOTE. Data for rifampin are from [1]; those for rifabutin, from [2]. C_{max} = maximum concentration; $t_{\frac{1}{2}}$ = elimination half-life; Cl_s = systemic clearance; F = bioavailability; pK_a = acid ionization constant (plasma); V_{ss} = volume of distribution (steady-state); and X_u = urinary recovery of unchanged drug.

* Values are mean (±SD).

† F assumed to be 100%: if F = 20%, V_{ss} = ~9 L/kg.

‡ Healthy volunteers.

Table 2. Ratio of rifabutin concentrations relative to plasma concentrations in tissues and body fluids of four surgical patients.

Tissue	Dose (mg)*	Tissue/plasma concentration (range) at indicated time after dosing†	
		6 h	12 h
Lung	150	1.4–8.6	5.6–6.8
Muscle	150	0.22–0.43	0.27–0.3
Bile	150	320–505	NA
Gallbladder	150	2–4.3	NA
Ileum	300	54‡	NA
Jejunum	300	93	NA

NOTE. Data are from [9, 10]. NA = undetectable in plasma and measurable in tissues at 48 hours.

* Three patients received the 150-mg dose, and one received the 300-mg dose.

† Ratios are based on the total antibacterial activity.

‡ At 8–9 hours after dosing.

Bioavailability Following Oral Administration of Rifabutin

In HIV-infected subjects who received oral capsules and, 1 hour later, a tracer dose of radiolabeled rifabutin intravenously, the oral bioavailability of a single dose was 20% [5]. In population sampling carried out during studies of prophylaxis for infection with *Mycobacterium avium* complex (MAC), the bioavailability was not affected by the presence of HIV disease [7]. The low bioavailability of rifabutin is probably due to high biliary excretion and substantial presystemic metabolism. Food decreases the rate, but not the extent, of absorption of rifabutin in the capsule formulation; this results in a lower C_{max} and a longer time to maximum plasma concentration (t_{max}) but no change in the area under the plasma concentration-vs.-time curve (AUC). Peak plasma levels are reached ~3 hours after oral dosing [4–6]. The C_{max} of rifabutin reached in plasma is low compared with that of rifampin. Following a 600-mg oral dose, the C_{max} of rifabutin is 0.4–0.6 μg/mL [5], while that of rifampin is 12–14 μg/mL [6].

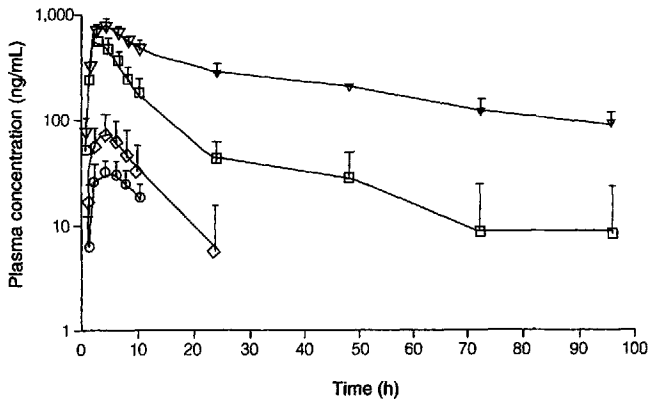

Figure 1. Plasma concentrations (mean ± SD) of rifabutin (—— □ ——) and its two major metabolites, 25-O-desacetyl rifabutin (—— ◇ ——) and 31-OH rifabutin (—— ○ ——), in healthy volunteers given a single dose of [^{14}C]rifabutin. The upper line (—— ▽ ——) shows the total ^{14}C counts/mL in plasma.

Clearance of Rifabutin

The information available on the clearance of rifabutin is limited. In a study of 15 healthy adults who received the oral capsule, oral clearance was 0.81 L/(kg·h) [4]. This figure is in agreement with an absolute clearance value of 0.14 L/(kg·h) and with an absolute bioavailability of 20% in HIV-infected patients who received the drug intravenously [5].

Protein Binding of Rifabutin

In vitro studies show that 72%–85% of rifabutin in plasma is bound to plasma proteins [5, 6]; this binding fraction remains constant over the therapeutic range of plasma concentrations. Rifabutin also can bind to plastics and permanently discolor soft contact lenses worn by patients taking the drug [8]. Although the binding to plastic should not cause a problem when an oral formulation of the drug (the only formulation currently marketed) is used, this characteristic should be considered when plasma samples have been stored for analysis of rifabutin concentrations.

Concentrations of Rifabutin in Tissues and Body Fluids

Rifabutin distributes extensively in various tissues, with tissue-plasma ratios ranging from >1 to almost 100 in samples from surgical patients (table 2) [9, 10]. Among five HIV-

Table 3. Pharmacokinetics of rifabutin (450 mg/d) after the dose and during multiple dosing in seven healthy volunteers.

	Pharmacokinetic parameter					
No. of doses	C_{max} (ng/mL)	AUC_{0-t}* (ng·h/mL)	t_{max} (h)	Cl_s/F (L/h·kg)	$t_{\frac{1}{2}}$, λ_z (h)	C_{max}(M1) (ng/mL)
1	691	9,287	2.3	0.7	45	86
10	613	5,803†	2.7	1.1†	58	47‡

NOTE. Values are mean (±SD). AUC = area under the plasma concentration-vs.-time curve; C_{max} = maximum concentration; Cl_s = systemic clearance; F = bioavailability; M1 = 25-O-desacetyl rifabutin; t_{max} = time to maximum plasma concentration; $t_{\frac{1}{2}}$ = elimination half-life.

* $t = \infty$ (1 dose) and 24 hours (10 doses).

† $P < .05$.

infected patients who received oral rifabutin at a dosage of 450 mg/d, concentrations of the drug in CSF (mean concentration, 47 ng/mL; range, 27–70 ng/mL) averaged 50.4% of those in serum (mean concentration, 93 ng/mL; range, 65–136 ng/mL) [11]. Because of the extensive redistribution of rifabutin in the tissues, the minimum plasma concentrations 24 hours after oral dosing are ~10%–15% of peak concentrations [5].

Multiple Dosing with Rifabutin

When rifabutin is administered chronically, it induces its own metabolism. Seven healthy volunteers received 450 mg of the drug daily for 10 days; a 38% decrease in the AUC and a 45% decrease ($P < .05$) in expected mean serum concentrations of the 25-O-desacetyl metabolite were observed (table 3) [2]. In a study of 15 HIV-infected patients receiving a daily dosage of 300–1,200 mg, the AUC (normalized for dose) was decreased by a mean of 42% from day 1 to day 28. The extent of this autoinduction response did not seem to be dose dependent [5]. Thus, HIV disease does not seem to have an important effect on this autoinduction phenomenon (*t* test, $P > .05$; 45% decrease in the AUC in healthy volunteers vs. a 42% decrease in HIV-infected patients).

Rifabutin induces hepatic microsomal enzymes, although to a lesser extent than does rifampin (CYP3A4 may be the hepatic cytochrome most sensitive to this effect). Among eight healthy volunteers, administration of oral rifabutin (300 mg for 7 days) resulted in a 29% increase in antipyrine clearance compared with the clearance after the first dose. This contrasts with the 90% increase in antipyrine clearance in the same subjects when they were given 600 mg of rifampin every day for 7 days [12].

Pharmacokinetics of Rifabutin in Different Populations

Use of rifabutin in men vs. women. Data from nine studies [13] indicate statistically significant but modest differences between the pharmacokinetics of rifabutin in men and women (table 4). When volume of distribution $(Vd_\lambda)/F$ values are normalized to the proportion of body fat in order to adjust for differences in the body compositions of men and women, the difference between the volume of distribution in men and that in women was not significant ($P = .3$) (P. K. Narang, personal communication). The differences that have been noted are probably not clinically significant, even assuming that the AUC and the C_{max} are correlated with activity [14].

Use of rifabutin in children and the elderly. Rifabutin has been used to treat MAC infection in a small number of children. The plasma concentration profile is reported to be similar to that for adults, with similar evidence of autoinduction (following multiple dosing, lower concentrations are observed on day 30 than on day 1). After a single dose of rifampin is given to children, the pharmacokinetic parameters are similar to those in adults. The $t_{1/2}$ appears to be slightly shorter in children; however, the concentrations after administration of the lower doses may be lower than the limits of detection of the assay, and the longer terminal elimination $t_{1/2}$ may be undetectable in these children. The adverse effects in children and adults appear to be similar [15] (P. K. Narang, personal communication).

Table 5 shows the C_{max}, AUC, and Cl_s/F in healthy elderly subjects in comparison with other populations. There were no

Table 4. Gender differences in rifabutin pharmacokinetics.

Pharmacokinetic parameter	Mean ± SD (no. of males)	Mean ± SD (no. of females)	*P* value
C_{max} (ng/mL)	450 ± 182 (65)	551 ± 255 (35)	.045
$AUC_{0-\infty}$ (μg·h/mL)	6.1 ± 2.7 (64)	7.8 ± 4.4 (35)	.044
Vd_λ/F (L/kg)	32 ± 19 (55)	53 ± 36 (30)	.038
$Vd_\lambda/F \cdot BF$* (L/kg)	32 ± 19 (55)	28 ± 19* (34)	.309

NOTE. Data are from [13]. Values are means (±SD) from nine studies. AUC = area under the plasma concentration-vs.-time curve; BF = body fat; C_{max} = maximum concentration; F = bioavailability; Vd = volume of distribution.

* Normalized to body fat.

Table 5. Mean pharmacokinetic values after oral dosing of rifabutin (300 mg) in different populations.

Population	Pharmacokinetic parameter		
	C_{max} (ng/mL)	AUC (ng·h/mL)	Cl_s/F (L/h·kg)
Healthy volunteers (*n*)	461 (34)	6,191 (29)	0.69 (46)
Subjects with hepatic disease (*n*)	472 (45)	8,159 (51)	0.76 (55)
Elderly subjects (*n*)	525 (36)	8,844 (43)	0.88 (118)
HIV-infected subjects (*n*)	381 (75)	5,324 (29)	0.84 (27)‡
Subjects with indicated level of renal dysfunction*			
Mild (*n*)	386 (27)	3,710 (31)†	1.37 (25)§
Moderate (*n*)	471 (41)	5,236 (46)	1.02 (75)
Severe (*n*)	470 (33)	6,328 (25)	0.90 (52)

NOTE. Data are from [10] and P. K. Narang (personal communication). All values have been normalized from 450 mg. AUC = area under the plasma concentration-vs.-time curve; C_{max} = maximum concentration; Cl_s = systemic clearance; F = bioavailability.

* Mild = creatinine clearance, 61–74 mL/minute; moderate = creatinine clearance, 30–42 mL/minute; severe = creatinine clearance, 8–29 mL/minute.

† $P < .05$, relative to healthy volunteers.

‡ Cl_s (iv) adjusted for bioavailability and body weight.

§ $P < .01$, relative to healthy volunteers.

statistically significant differences in these pharmacokinetic values [10] (P. K. Narang, personal communication).

Use of rifabutin in patients with hepatic disease, renal dysfunction, or HIV infection. The mean values for the C_{max}, AUC, and Cl_s/F in patients with hepatic disease were not significantly different from those in healthy volunteers. However, among patients with severely impaired liver function (Child Pugh score, ≥10), there was a significant increase in AUC values (P. K. Narang, personal communication), suggesting that doses of the drug may need to be reduced [16]. Among patients with renal dysfunction, the only values that differed significantly from those among healthy volunteers were the AUC and Cl_s/F in patients with mild renal dysfunction (table 5). There is no obvious explanation for these findings, and these differences appear to reflect a statistical aberration rather than an important difference in patients with mild renal dysfunction.

The data indicate that the pharmacokinetics of rifabutin in HIV-infected subjects do not differ from those in healthy persons (table 5).

Interactions Between Rifabutin and Other Drugs

Some of the most important questions about the pharmacokinetics of rifabutin concern its interactions with other drugs used in the treatment of the immunocompromised patients who are the primary candidates for treatment or prophylaxis with rifabutin.

Antiretroviral Agents

Zidovudine. The C_{max} of zidovudine, which is eliminated primarily via glucuronidation by a hepatic glucuronosyl transferase, is decreased by ~48% in patients receiving chronic treatment with rifabutin (figure 2A), and there is a 32% reduction in the AUC of zidovudine [17]. However, no clinical effects of these reduced values have been noted [18]. Zidovudine, however, has no effect on the pharmacokinetics of rifabutin (figure 2B) [19].

Didanosine. Because didanosine is eliminated primarily via the renal route, rifabutin does not alter the pharmacokinetics of didanosine [20].

Antimicrobial Agents

Isoniazid. Rifabutin administered at a dosage of 300 mg/d for 9 days had no effect on the plasma pharmacokinetic profiles of isoniazid or acetylisoniazid [21].

Clarithromycin. The interaction between rifabutin and clarithromycin appears somewhat complex (table 6) [22]. Rifabutin was administered to subjects on days 0–42, and clarithromycin was administered on days 15–42. On day 42, the rifabutin AUC was about twice what it was on day 14, which is a statistically significant difference. This increase is probably due to the inhibition of rifabutin metabolism by clarithromycin. Chronic administration of rifabutin results in significantly lower concentrations of clarithromycin and an increase in the clarithromycin metabolite 14-OH clarithromycin on day 42 (R. Hafner and P. K. Narang, personal communication). It is likely that induction of clarithromycin metabolism is involved in this interaction. Since 14-OH clarithromycin is active as an antimicrobial, the clinical significance of the effect on clarithromycin is unknown.

Fluconazole. The C_{max}, t_{max}, and AUC of fluconazole are essentially unchanged by the presence of rifabutin [23]. How-

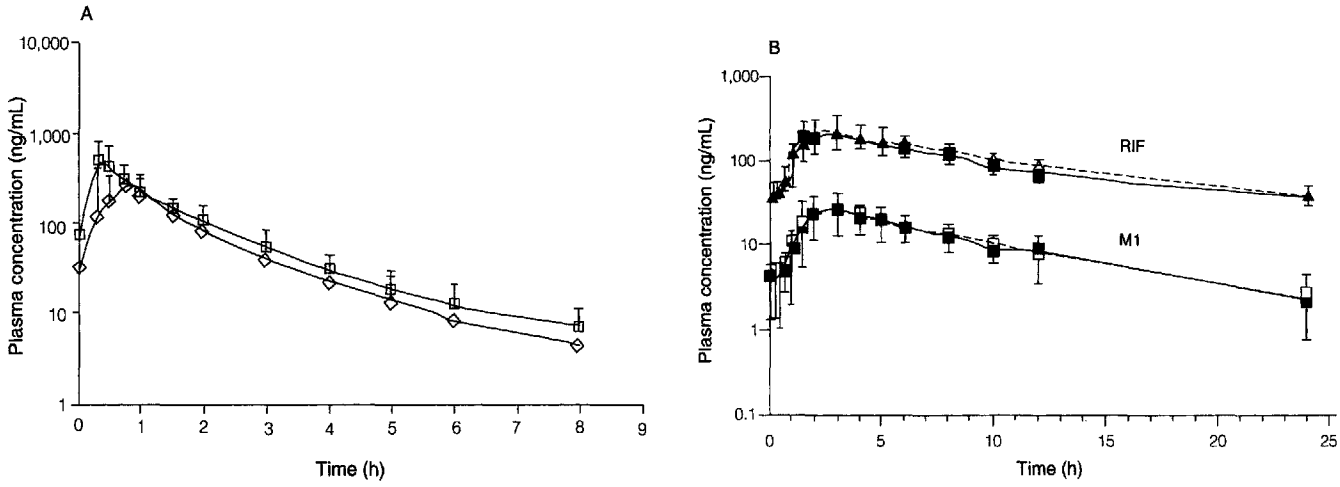

Figure 2. Effect of combined administration of rifabutin (RIF) and zidovudine (ZDV) on steady-state concentrations of both drugs in HIV-infected patients. *A*: Mean concentrations of ZDV (300 mg once daily; n = 8) administered alone (—— □ ——) and after 13 days of coadministration with rifabutin (—— ◇ ——); *B*: mean concentrations of rifabutin (RIF) (—— ▲ ——, day 13; ---- △ ----, day 16) and its metabolite 25-OH-desacetyl rifabutin (M1) (—— ■ ——, day 13; ---- □ ----, day 16) after 13 days of coadministration with ZDV and after 3 days without coadministration of ZDV (day 16) (n = 12).

ever, because fluconazole inhibits hepatic microsomal P-450 enzymes, it has an important impact on the pharmacokinetics of rifabutin. The increases in the C_{max} and AUC of rifabutin and the decrease in the Cl/F in patients receiving fluconazole are highly significant (table 7) [24]. In fact, in a protocol for MAC prophylaxis, the incidence of the development of MAC bacteremia was lower among patients who received the combination of fluconazole and rifabutin than among those who received placebo plus rifabutin [25]. Among HIV-infected patients who received rifabutin prophylaxis, 16 (5.9%) of the 272 patients who received fluconazole and 32 (10.9%) of the 294 patients who did not receive fluconazole developed MAC bacteremia ($P < .033$). In the placebo group (no rifabutin), there were no differences between the patients who received fluconazole and those who did not in terms of the incidence of bacteremia (17.2% vs. 17.9% of patients, respectively $P = .819$).

Other Drugs

Methadone. There have been reports of mild symptoms of withdrawal in 3 of 27 patients enrolled in rifabutin studies who were receiving methadone maintenance therapy [26].

Cyclosporine. Rifabutin had less of an effect than did rifampin on the disposition of cyclosporine in one renal transplant recipient [27].

Conclusion

Rifabutin and rifampin are structurally similar, yet the two drugs have different pharmacokinetic profiles and are distributed differently in tissues. Rifabutin has a relatively slow distribution and a large volume of distribution, which results in a high C_{max} and a long terminal elimination $t_{1/2}$. Rifabutin appears to be a less potent inducer than is rifampin, although the induc-

Table 6. Effect of concomitant administration of rifabutin and clarithromycin on area under the plasma concentration-vs.-time curves (AUCs) of the two drugs and of a clarithromycin metabolite in HIV-infected subjects.

Drug (n = no. of subjects)	AUC (μg · h/mL) on indicated day*			P value
	Day 14	Day 15	Day 42	(day 14 vs. day 42)
Rifabutin (n = 14)	3,895 ± 1,498	5,846 ± 1,882	7,096 ± 2,586	<.05
Clarithromycin (n = 11)	38.0 ± 15.1	36.3 ± 15.9	17.1 ± 6.7	.002
14-OH Clarithromycin (n = 11)	9.4 ± 3.5	9.4 ± 3.8	13.4 ± 5.1	.006

NOTE. Data are from [22] and R. Hafner (personal communication). Values are mean (±SD). Rifabutin (300 mg daily) was administered on days 0–42; clarithromycin (500 mg twice daily) was administered on days 15–42. The mean CD4 cell count was 86/mm^3 (median, 65/mm^3).

* Day 14 = administration of rifabutin but no clarithromycin; day 15 = day 1 of rifabutin plus clarithromycin; day 42 = day 28 of rifabutin plus clarithromycin.

Table 7. Pharmacokinetics of rifabutin with and without coadministration of fluconazole in 12 subjects.

Drug(s) administered	Pharmacokinetic parameter			
	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (ng · h/mL)	Cl/F (L/h · kg)
Rifabutin + fluconazole	507 ± 248	2.9 ± 0.8	5,282 ± 2,330	0.85 ± 0.40
Rifabutin alone	308 ± 185	3.0 ± 1.0	3,063 ± 1,080	1.40 ± 0.69
P values	.008	NS	.0007	.006

NOTE. Data are from [23, 24]. Values are mean (±SD). AUC = area under the plasma concentration-vs.-time curve; C_{max} = maximum concentration; Cl = clearance; F = bioavailability; NS = not significant; t_{max} = time to maximum plasma concentration.

tion by rifabutin of its own metabolism results in decreases in plasma concentrations when it is given in multiple doses. The diminished enzyme-inducing properties of rifabutin may lead to fewer potential drug-drug interactions than are seen with rifampin [6].

Factors such as age, gender, and renal function do not appear to have any clinically significant effects on the pharmacokinetics of rifabutin. However, rifabutin should be administered cautiously to patients with severe liver disease.

More studies are needed to establish the highest dose of rifabutin that is well tolerated for the prolonged periods of treatment required for most mycobacterial infections. Because of the unique distribution of rifabutin in tissues, further studies of different treatment schedules seem warranted. In addition, more studies are necessary to establish the role of rifabutin in combination therapy for MAC infections [28].

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Discussion

DR. MICHAEL TAPPER. Are there any additional data on the interaction between rifabutin and some of the other drugs—specifically itraconazole or azithromycin—commonly used in HIV-infected patients?

DR. TERRENCE F. BLASCHKE. There is no information at present, but one of the major projects of the AIDS Clinical Trials Group (ACTG) with which I am involved is to look specifically at a number of interactions of drug combinations that have been proposed for treatment of multiple opportunistic infections. These are important questions, and data will be generated. Many of these studies may be under way.

PASQUALE CETERA. Dr. Richard Hafner is directing an ongoing study of azithromycin, which is supposed to finish accrual by the end of 1994. We hope we'll have the data next year. Dr. Carol Trapnell is conducting an ongoing study of dapsone and rifabutin, and Dr. Paul Sullam has just finished a study of trimethoprim-sulfamethoxazole and rifabutin. We are initiating a study on the interaction of rifabutin and rifampin with oral contraceptives, which has been requested by the U.S. Food and Drug Administration.

DR. BLASCHKE. Are you evaluating itraconazole or any antiretroviral agents?

CETERA. No, not yet.

DR. FRED M. GORDIN. The other drug that will probably become important is oral ganciclovir, which Syntex Laboratories (Palo Alto, CA) has now stated is effective in preventing retinitis in roughly the same population of persons with low levels of CD4 cells.

DR. BLASCHKE. With all these drugs, the possible number of drug interactions becomes high. We in the pharmacology program and the ACTG program are trying to provide as much rationalization as possible for prioritizing those drug interactions that need to be studied. We could study all of them, but we would use up all the resources of Pharmacia and perhaps the ACTG, which would not be appropriate.

DR. CALVIN M. KUNIN. You are raising a very important question because most of the patients receiving rifabutin are taking four drugs, six drugs, or even more. You can't just study two drugs; you have to study four or six because they all relate to one another. In addition, there are variations in dosages and compliance. It's obviously impossible to do all these studies.

DR. BLASCHKE. It's difficult, but it may not be impossible. One of the approaches we are using, at least in the multiple-drug protocols that are part of the ACTG program, is that of random population sampling to identify those combinations that deserve a more intensive study of pharmacokinetic interaction. I think that is the best we can do. It is difficult looking at two-drug combinations; three- four-, and five-drug combinations are even more complicated. But I think predicting drug interactions is not as outrageous as it might sound. We're getting much better at understanding the in vitro and in vivo correlations regarding drug interactions. There are some animal models and in vitro systems that allow us to look at these correlations and focus on the studies of drug combinations and interactions that should actually be done in the clinic. There will always be an unexpected interaction popping up along the way, but we have to consider the resources used in these combination studies.

DR. RICHARD E. CHAISSON. You and your colleagues presented an interesting study at one of the ACTG meetings on compliance with the ACTG 175 protocol, which showed, not unexpectedly, that compliance with study medications was quite variable. Do you think that some of the data you showed on drug interaction might have been influenced by compliance with this protocol, which consisted of treatment courses that required up to 42 pills per day? Can you speculate on the effect of intermittent compliance on the pharmacokinetics of erythromycins in particular or on other hepatic enzyme inducers in general when patients take them from time to time rather than consistently? How will this affect the drug interactions?

DR. BLASCHKE. Those are good questions. I don't think that compliance is a major factor in these studies; they are short and highly focused pharmacokinetic studies, so the compliance is probably adequate. There is a dose-response curve, as I tried to illustrate with regard to the autoinduction response observed with chronic administration of rifabutin. We may already have reached the top of the curve, even with the doses of rifabutin used clinically, so we don't see that dose-response relationship. Your question is more interesting in terms of how little drug is actually necessary to produce enzyme induction and whether a half-time personal dosing schedule would impact on this induction. What is the minimum amount of rifabutin necessary for induction? We don't know. We are interested in rifabutin dosing and in trying to relate drug exposure to both clinical outcome and antiretroviral therapy. The interaction studies that are going to be done fairly soon include compliance as a potential explanatory variable in some of the studies of mycobacteria. As part of those protocols, we're doing a combination of intensive interaction studies in addition to looking at compliance. I think your colleague at Johns Hopkins Medical School, Dr. Charles Flexner, is evaluating clarithromycin in one study.

BEN CHENG. I know of one other drug interaction study that has been completed. It was done by Upjohn (Kalamazoo, MI) with delavirdine, which is this company's nonnucleoside reverse transcriptase inhibitor. They found that rifabutin decreased area-under-the-curve (AUC) levels of delavirdine by ~30%–35%, whereas rifampin decreased delavirdine AUC levels by ~95%. However, I don't know what effect delavirdine has on levels of rifabutin or rifampin.

DR. BLASCHKE. It would be interesting to know whether these interactions could be predicted by what we know about delavirdine metabolism. It's important to establish in vitro–in vivo correlations for these interactions. Otherwise, we are faced with enormous problems about what to study clinically. The correlations I have seen have actually been quite good.

DR TAPPER. In my naive way, I tend to think of drug interactions as happening once both drugs are absorbed into the body. Clearly, a different set of problems causes malabsorption—with drugs simply not being absorbed. In the ACTG studies, as well as others, you're looking at some of these drug interactions as functions of CD4 cell counts related to HIV disease progression, and, obviously, most of the patients who are getting prophylaxis or treatment for disease due to *Mycobacterium avium* complex (MAC) have lower CD4 cell counts. A significant degree of diarrhea and malabsorption occurs in such patients.

DR. BLASCHKE. Outcome has been looked at in relation to disease severity and CD4 cell count. Dr. Narang might want to comment about the effects in patients with diarrhea or malabsorption.

DR. P. K. NARANG. We have not looked specifically at diarrhea as an outcome variable. Using our available data base, we might have to look at whether there's a difference in absorption of rifabutin. What we did was based on CD4 cell counts. We split the data we had collected during the Pharmacia MAC prophylaxis study—the population data base you have seen for zidovudine. We also have a similar data base for rifabutin levels.

DR. BLASCHKE. I think that the absorption of highly lipid-soluble drugs like rifabutin is usually not limited by diarrhea; it is not likely to be a major cause of decreased absorption. It is now understood that the gut possesses fairly high concentrations of certain cytochrome P-450 enzymes, which may make an important contribution to the first-pass metabolism of many drugs. That is another area that should be looked at in much more detail, not just in terms of rifabutin, but in terms of other drugs.

DR. PAUL A. SULLAM. Given the long half-life of rifabutin, could it be administered less frequently and thus have different interaction kinetics with drugs like clarithromycin? In other words, is there perhaps again a threshold for induction, or is it strictly a concentration phenomenon?

DR. BLASCHKE. As I said before, there is a dose response, and I think we have exceeded it with the current therapeutic doses. Changing the dosing regimen probably wouldn't influence the dose response significantly. It might change, as Dr. Chaisson mentioned earlier, if people took less drug; however, I think that a dose response occurs at the doses that are probably near the top of the response curve with respect to induction of P-450 enzymes. A decrease in the dosing frequency, such as Dr. Sullam suggests, would have more of an impact on the antimicrobial efficacy of the drug than on drug interactions. Some issues here are worth considering in terms of designing trials for efficacy. But there will be a modest amount of enzyme induction no matter how the drug is given, which is not a problem; you just adjust the doses.