Utility of Rifampin Blood Levels in the Treatment and Follow-up of Active Pulmonary Tuberculosis in Patients who Were Slow to Respond to Routine Directly Observed Therapy

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Utility of Rifampin Blood Levels in the Treatment and Follow-up of Active Pulmonary Tuberculosis in Patients who Were Slow to Respond to Routine Directly Observed Therapy*

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Study objective: **The standard daily dose of rifampin in directly observed treatment of *Mycobacterium tuberculosis* (TB) is 600 mg, taken orally. The purpose of this study was to assess the efficacy of standard dose rifampin therapy in patients who were slow to respond to routine directly observed therapy (DOT).**

Methods: **Patients with non-drug-resistant pulmonary TB who were receiving 600 mg of oral rifampin by DOT were eligible for inclusion. Patients were deemed slow to respond if their sputum smears and cultures remained positive for *M tuberculosis* and if the patient's condition did not improve clinically or radiographically after 3 months of treatment. Serum rifampin levels were ascertained to determine the adequacy of the standard rifampin dosing. Patients with subtherapeutic blood levels had their rifampin dose increased to 900 mg, and rifampin levels were repeated. Rifampin dosage was increased again if blood levels were still subtherapeutic. No antitubercular medications were added to the treatment regimen. The total weekly dose of the other standard treatment drugs was not increased.**

Results: **Of 124 new patients with active pulmonary TB, 6 patients were identified as slow to respond to the standard antitubercular DOT. All six patients had subtherapeutic serum rifampin levels. All six patients responded clinically, radiographically, and mycobacteriologically after an increase in rifampin dosage to reach target drug blood level.**

Conclusions: **Standard dosing with rifampin resulted in a poor clinical response and subtherapeutic serum levels in six patients. Increasing the dosage of rifampin improved the outcome without additional side effects. In TB patients who are slow to respond to standard treatment, an inadequate dose of rifampin should be suspected. Current antituberculer drug administration does not include adjusted dosage for rifampin.** ***(CHEST 2001; 120:1520–1524)***

Key words: pulmonary tuberculosis; rifampin blood levels

Abbreviations: CXR = chest radiographs; DOT = directly observed therapy; ETH = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; TB = tuberculosis

Tuberculosis (TB) is a readily curable disease when adequate antitubercular treatment is administered in a timely manner. Cure rates of > 95% are achieved with standard short-course chemotherapy regimens for non-drug-resistant strains of TB.[1] Treatment failures are attributed to delayed disease detection or treatment, noncompliance, multidrug resistance, HIV infection, and other comorbidities.[2,3] Patients without these risk factors are expected to respond well to treatment. Moreover, directly observed therapy (DOT) has been instituted as a method to enhance patient adherence and to decrease treatment failures, relapses, and the emergence of acquired drug-resistant organisms. Recent reports, however, have described patients without markers for adverse outcomes who nevertheless responded poorly to appropriate treatment. The adverse outcome was attributed to subtherapeutic antitubercular drug levels in each of these patients.[4–7]

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Patients with pulmonary TB who have been receiving appropriate antitubercular therapy for 3 months without clinical or chest radiographic (CXR) improvement and whose expectorated sputum continues to harbor *Mycobacterium tuberculosis* organisms are considered to be slow to respond. We undertook this study to investigate the role that subtherapeutic blood rifampin levels may be playing in this subset of patients.

Materials and Methods

All new adult patients with expectorated sputum smear and culture-positive active non-drug-resistant pulmonary TB, who were followed at the Memphis and Shelby and the Washington Counties Health Departments from August 1997 to August 1999, were eligible for inclusion in this study. During this time period, it was the practice at both of these health departments to initiate standard four-drug DOT to all patients not suspected of having drug-resistant pulmonary TB. All patients who were eligible for study were, therefore, initially treated orally with isoniazid (INH) 300 mg/d, rifampin (RIF) 600 mg/d, pyrazinamide (PZA) 25 mg/kg/d, and ethambutol (ETH) 25 mg/kg/d. Therapy with four drugs was continued for 2 months. After 2 months, patients were treated with INH and RIF alone for 4 additional months or until the patient's sputum was smear negative and culture negative for two consecutive reports. These medications were received daily for 1 month and then twice a week. The total weekly dosages for INH, PZA, and ETH remained the same on the twice weekly treatment regimen. The dose of RIF was not increased but remained at 600 mg each day that DOT was delivered on the twice weekly regimen as recommended by the Centers for Disease Control and Prevention and by the American Thoracic Society.[8]

Patients were seen by a physician on a monthly basis and had eye examinations, CXRs, serum liver function tests, and albumin levels determined with each office visit. Expectorated sputum was stained for acid-fast bacilli and cultured monthly. Patients were deemed slow to respond if the patient's condition had not improved clinically, if they failed to show radiographic improvement on CXR, and if their sputum smears and cultures remained positive for *M tuberculosis* after 3 months of treatment. Since 1997, all new *M tuberculosis* isolates in Tennessee undergo drug sensitivity testing. Patients with drug-resistant TB were, therefore, easily identified and excluded from analysis.

Serum RIF levels were ascertained in the patients who were slow to respond to determine the adequacy of standard RIF dosing. No other drug blood levels were assessed because the patients received higher dosages of the other antitubercular drugs once the twice weekly DOT was initiated. The RIF dosage was not increased when twice weekly therapy was started and remained at 600 mg on those 2 days. Serum RIF levels were drawn 1 ½ to 2 ½ h after directly observed ingestion of oral RIF, taken while the patients were fasting. The blood specimens were then centrifuged, and 5 mL of serum was frozen immediately and sent to a state-approved reference laboratory for measurement of RIF levels (MRL Reference Laboratory; Cyprus, CA). The specimens were analyzed according to previously published recommendations.[9] The RIF levels were determined by high-performance liquid chromatography. The reference laboratory ran control samples and followed state-approved guidelines for reproducibility of the drug levels. High and low level controls and one blind control were run each time a patient's sample was tested. Computer-automated 10-point curves were obtained with a range of 0.1 to 32 μg/mL. Drug-to-drug interactions in the assay method were tested for INH, PZA, and ETH. Presence of any of these drugs did not alter the results of serum RIF levels.

A serum RIF level between 8 and 24 μg/mL was considered therapeutic.[10] The dose of RIF was increased to 900 mg for patients with serum RIF levels below the therapeutic range. RIF serum levels were then repeated. RIF dosage was increased again if the second RIF level was subtherapeutic, and a third RIF serum level was performed. No other antitubercular drugs were added and no other dosages were increased in patients who were slow to respond.

Patient demographic data, physical examination findings, results of expectorated sputum acid-fast stains and cultures, response to purified protein derivative skin tests, CXR findings, and laboratory data were recorded. The patients' medical histories and concomitant medications, including herbal and holistic remedies and over-the-counter drugs, were reviewed to identify comorbid conditions or drugs that might effect RIF pharmacokinetics. The patients were also questioned about symptoms of malabsorption. The time, measured in weeks, at which the patients were deemed slow to respond was recorded. Once the patients' RIF dosage was increased, the time (in weeks) to a clinical improvement was recorded. Patients continued to be followed up after completion of their antitubercular therapy to assess for relapse.

Results

During the study period, 124 new adult patients with non-drug-resistant pulmonary TB were started on a regimen of antitubercular therapy. Six of these patients were slow to respond to standard DOT. The average age of these six patients was 50.7 years (Table 1). There were five men and one woman. Three of the patients tested positive for purified protein derivative. All of the patients had upper lobe infection from *M tuberculosis*. The mean time after initiation of antitubercular therapy at which the patients were deemed slow to respond was 19 weeks.

The initial serum RIF levels of all six patients who were slow to respond to standard antitubercular therapy (RIF dose at 600 mg) were subtherapeutic (Table 2). Retesting the patients' RIF blood levels after increasing their RIF dose to 900 mg resulted in therapeutic levels for all but one patient. This patient required titration of his RIF dose to 1500 mg to keep his RIF level in the therapeutic range. The average time to clinical response after adjusting the RIF dosage was 5.33 weeks. Patient compliance with medication was not an issue in this study because DOT was used.

Three patients were alcoholics. The clinicians described these patients as moderate consumers of alcohol. One patient was infected with HIV. This patient was taking a reverse transcriptase inhibiting drug (zidovudine) as well as prophylactic antibiotics (difluconazole, azithromycin, and trimethoprim/sulfamethoxazole). He was not receiving a protease inhibitor. All six patients denied using herbal and holistic preparations and over-the-counter medica-

Table 1—*Demographic Data of Patients Who Were Slow to Respond to Antitubercular Therapy

Patient No.	Age, yr/Sex	Smear/Culture	PPD	CXR	Comorbid Illness	Clinical Failure, wk†	Clinical Response, wk†
1	56/m	+/+	−	Biapical infiltrate	None	12	4
2	68/m	+/+	+	Biapical infiltrate	Alcoholism	14	8
3	42/f	+/+	+	Left upper lobe infiltrate	None	22	4
4	60/m	+/+	+	Left upper lobe cavity with biapical infiltrate	Alcoholism	24	8
5	40/m	+/+	−	Left upper lobe cavity with biapical infiltrate	Alcoholism	24	4
6	38/m	+/+	−	Right upper lobe infiltrate	HIV‡	18	4

*m = male; f = female; PPD = purified protein derivative.
†After adjusting rifampin dose.
‡Patient taking oral zidovudine, sulfamethoxazole/trimethoprim, azithromycin, and difluconazole.

tions. No symptoms of malabsorption were noted by any of the six study patients, and their serum albumin levels were normal.

All six study patients successfully completed their antitubercular therapy. There were no adverse outcomes or reactions caused by the increase in their RIF dosages. None of the *M tuberculosis* organisms isolated from the six study patients demonstrated an acquired drug resistance during this study. None of the isolates demonstrated a change in their minimal inhibitors concentration to RIF. There have been no known cases of relapse of the study patients' *M tuberculosis* pulmonary infection.

Discussion

Most published studies on the pharmacokinetics of RIF were performed on healthy volunteers or were treatment studies in patients with drug-susceptible TB. Maximum RIF serum concentration is typically reached 2 h after oral administration, and its normal half-life in humans is 2 to 4 h. The volume of distribution of RIF is 0.6 to 1.0 L/kg of body weight. It is 60 to 80% protein bound. The liver clears 90% of RIF from the body, and the kidney clears 10% of RIF.[10,11] The dosage of RIF has been, therefore, standardized for all patients except those with severe hepatic or renal disease.

Subtherapeutic antitubercular blood drug levels including RIF have been observed in the HIV-positive population.[12–16] These reports emphasize that achieving therapeutic serum drug concentration is important for clinical efficacy of antitubercular treatment in the HIV-infected patient. Therapeutic drug monitoring, therefore, has been advocated in patients who are HIV positive and are undergoing treatment for pulmonary TB. Therapeutic antitubercular serum concentrations also offer the best chance for rapid cure in patients who are not infected with HIV.

Therapeutic drug monitoring is the process of adjusting drug doses based on serum concentration determination.[10] Therapeutic drug monitoring allows for better control of antitubercular therapy, and its use has been encouraged in the treatment of pulmonary TB in patients with significant comorbid conditions, such as end-stage liver or renal disease and HIV infection. Serum concentrations provide objective data regarding how selected doses are meeting therapeutic goals. Drug therapy is the main aspect of TB infection that is within the control of the physician. Other variables such as patient demographics, extent and duration of disease, comorbid illnesses, and drug susceptibility are predetermined. If the physician can provide optimal treatment, it is hoped that patients will respond better to therapy.

For most patients, the standard RIF dosage is adequate.[10] Standard dosing results in subtherapeutic blood levels in only a subset of patients. It is toward this subset of patients that the public health system needs to direct its efforts. Our data suggest that therapeutic drug monitoring is a useful tool in

Table 2—*Rifampin Blood Levels*

Patient No.	Rifampin, 600 mg (μg/mL)	Rifampin, 900 mg (μg/mL)	Rifampin, 1500 mg (μg/mL)
1	1.5	9.2	–
2	5.9	14.4	–
3	< 1.0	9.9	–
4	< 1.0	1.04	20.28
5	< 1.0	13.8	–
6	3.54	15.21	–

the treatment protocol in patients who are slow to respond to standard antitubercular treatment. Because five of our patients were HIV negative, RIF blood levels appear to be helpful on a case-by-case basis even in patients who are not infected with HIV.

Poor absorption of the antitubercular medications through the GI tract is believed to be the mechanism resulting in subtherapeutic drug levels in the pulmonary TB patient.[12–15] Proposed mechanisms for antitubercular drug malabsorption include cytokine destruction of bowel villi, undiagnosed GI TB, bacterial overgrowth, and preexisting celiac disease.[6] Although drug malabsorption is usually not associated with celiac disease, poor drug absorption has been documented with RIF.[17] Whereas poor drug absorption may occur even in the absence of malabsorptive symptoms, other possibilities for the low RIF levels observed in our patients include the genotypic make-up of their cytochrome P-450 system and induction of the cytochrome CYP2C9 by alcohol in three of our patients. Drug interactions appear to be unlikely in all but one of our patients because they repeatedly denied the use of herbal and over-the-counter medications. Drug/food interaction also seems an unlikely explanation for our patients because they were fasting at the time their serum RIF levels were drawn.

In addition, patients with pulmonary TB are often malnourished. A poor nutritional status results in a fall in plasma concentration time curve of RIF and an increased renal clearance caused by a decrease in protein-bound drugs. If patients absorb only portions of their drug regimen, this, in effect, puts them on a regimen of fewer antitubercular drugs or even monotherapy. The latter condition may lead to the selection of drug resistance.[18] Persistently low drug concentrations may select for multiple drug resistance. Because initial mycobacterial drug sensitivities may change, it is essential to have analysis of mycobacterial sensitivities during treatment. None of the mycobacterial isolates obtained from our six study patients exhibited acquired drug resistance or a change in the concentration of minimal inhibitors.

Higher dose of RIF can cause a flu-like syndrome when given intermittently.[10] None of our patients reported these symptoms. In addition, results of liver function tests and eye examinations remained within normal limits in our study patients. Therefore, the higher dosages of RIF were well tolerated. Three of our patients with subtherapeutic blood RIF levels ingested alcohol on a daily basis. A recent report indicated that alcohol consumption can cause higher blood RIF levels.[5] The reason for these opposing observations is not clear but warrants further investigation.

One of the limitations of our study was that serum levels of the other antitubercular drugs, INH, PZA, and ETH, were not determined. However, given that the conditions of our patients who were slow to respond improved by adjusting only the RIF dosages strongly supports our hypothesis that low RIF levels contributed to the delayed responses seen in our patients. Another limitation was that serum RIF levels were determined in only those patients who were deemed to be slow to respond. Therefore, it is possible that the other patients who had responded as expected to standard antitubercular therapy had low serum RIF levels that went undetected. In addition, serum RIF levels were assessed at only one time interval (1 ½ to 2 ½ h) after oral ingestion in each of our patients. Therefore, we cannot rule out the possibility of delayed absorption in our patients. However, given the slow clinical response to standard therapy and improvement after adjusted dosing of RIF, we believe that delayed absorption is an unlikely explanation for the subtherapeutic RIF blood levels observed in our patients.

We did not observe any acquired resistance to RIF of other antitubercular drugs caused by the subtherapeutic RIF levels. Early studies showed that it takes, on average, 2 months to develop drug resistance to monotherapy.[19] Our patients received at least two drug therapies at all times; hence, the subtherapeutic RIF serum levels did not seem to increase the risk of drug resistance. However, this subject needs further investigation.

Malabsorption of RIF is an increasingly recognized problem that needs to be overcome for the successful treatment of TB. Standard-dose therapy works well for most patients with drug-susceptible TB. Most patients, therefore, do not require drug monitoring as long as they respond to therapy in a predictable manner. However, should the patient remain acid-fast bacilli smear positive after 3 months of DOT, therapeutic drug monitoring should be considered. Earlier intervention should be undertaken for patients with concomitant HIV infection, malnutrition, known GI or malabsorptive disease, and hepatic or renal disease.

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