Population Pharmacokinetics of Dapsone Administered Biweekly to Human Immunodeficiency Virus-Infected Patients

GIORGIO GATTI,1,* MARA MERIGHI,2 JAVAD HOSSEIN,1 SILVIA TRAVAINI,1 ROSETTA CASAZZA,1 MATS KARLSSON,3 MARIO CRUCIANI,2 AND DANTE BASSETTI1

First Department of Infectious Diseases, School of Medicine, University of Genoa, Genoa,1 and Department of Infectious Diseases, School of Medicine, University of Verona, Verona,2 Italy, and Department of Biopharmaceutics and Pharmacokinetics, University of Uppsala, Uppsala, Sweden3

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The population pharmacokinetics of dapsone were examined in human immunodeficiency virus-infected patients receiving dapsone at a dosage of 100 mg twice weekly for the prevention of Pneumocystis carinii pneumonia. Nonlinear mixed-effect modeling was used to determine the best pharmacostatistical model for the data. A one-compartment open model with first-order absorption and elimination was used as the structural pharmacokinetic model. Several covariates were tested for their influence on pharmacokinetic parameters. Rifampin was found to increase the values of clearance/bioavailability (CL/F) and volume of distribution/bioavailability (V/F) by approximately 70%. CL/F and V/F were 1.83 liters/h and 69.6 liters, respectively, for patients not taking rifampin. The effect of rifampin on the pharmacokinetic parameters of dapsone was appreciably less than expected on the basis of studies with healthy volunteers. Increased bilirubin levels were associated with a significant decrease in the absorption rate constant (Ka). However, this finding may be considered clinically irrelevant because the post hoc Bayesian estimates of Ka for patients with high bilirubin levels (>1.2 mg/dl) were at the lower bound of the values for patients with normal bilirubin levels. The value of Ka was 0.957 h^-1 for a patient with a bilirubin level of 0.7 mg/dl. After inclusion of covariates in the model, the interpatient variability was 35% for CL/F, not significant for V/F, and 85% for Ka. Simulation of plasma concentration-versus-time curves indicated that the administration of 100 mg of dapsone biweekly is associated with sustained dapsone levels in the plasma of the majority of the patients. Dosage adjustments for patients concomitantly treated with rifampin may be necessary.

Human immunodeficiency virus (HIV)-infected patients with low CD4+ lymphocyte counts are at high risk for developing Pneumocystis carinii pneumonia (PCP). Trimethoprim-sulfamethoxasole (TMP-SMX) is considered the agent of first choice for the prophylaxis of PCP. However, the high rate of adverse effects represents a limiting factor to the extensive use of this drug. Aerosolized pentamidine is indicated by the Centers for Disease Control and Prevention as an alternative to TMP-SMX. However, it is associated with a high relapse rate (5 to 25%) and does not protect recipients from extrapulmonary infection.

The experience with dapsone as an agent for PCP prophylaxis in HIV-infected patients has been increasing over recent years. Dapsone has been tested as an agent for PCP prophylaxis at different dosage regimens, namely, 50 to 100 mg daily (4, 16, 18, 22), 100 mg twice or thrice weekly (6, 7, 29, 31), and 100, 200, or 300 mg once weekly (1, 11, 17, 21, 25, 27). Even though the comparability of these investigations is hindered by such variables as disease stage at study entry, duration of follow-up, concomitant anti-HIV therapy, primary versus secondary prophylaxis, and risk factor, it appears that a daily dosage may be more effective but may be associated with higher rates of adverse reactions than weekly dosage regimens, while weekly regimens may be associated with lower rates of adverse effects and a higher incidence of treatment failures than daily regimens. It also appears that between- and within-study variabilities are high. Variability in clinical outcome may be a consequence of variability in pharmacodynamics or pharmacokinetics, or both. The characterization of the sources of pharmacokinetic variability may serve as a basis for optimization of the dosage regimen. To date, only one study describing the pharmacokinetic aspects of dapsone in HIV-infected patients following the administration of single and multiple doses of 200 mg per week has been published (11). The study included a limited number of patients and did not allow for the extensive evaluation of the effects of covariates on pharmacokinetic parameters. In two other reports (19, 25), the concentrations of dapsone in the plasma of HIV-infected patients were determined without estimation of pharmacokinetic parameters.

Our investigation aimed at the evaluation of the population pharmacokinetic parameters of dapsone in HIV-positive patients receiving 100 mg of dapsone twice weekly for PCP prophylaxis.

MATERIALS AND METHODS

The study was approved by the institutional committee for human research of each of the institutes participating in the study. Written informed consent was obtained from the patients before their enrollment in the study.

Two medical centers participated in the study. Eleven patients were observed at center 1, and 42 patients were observed at center 2. Patient demographics are presented in Table 1.

Patients were enrolled in the study if they had CD4+ lymphocyte counts of ≤200 cells per μl. For some patients, the CD4+ cell levels at the time of the pharmacokinetic study were greater than 200 cells per μl. A complete medical history, a physical examination, and a panel of laboratory tests consisting of a chemistry screen and a complete blood cell count with differential and platelet count were available within a week of the pharmacokinetic study. The medications administered concomitantly or within 2 weeks before the first study day were recorded.

Each patient received a 100-mg dose of dapsone twice a week orally. At center 1, 100-mg tablets manufactured by Farmitalia-Carlo Erba (Milan, Italy) were used, whereas at center 2, the dapsone doses were manufactured by the hospital.
patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>33 (27–46)</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>62 (40–83)</td>
</tr>
<tr>
<td>Ht (cm)</td>
<td>172 (150–190)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.58 (1.04–1.96)</td>
</tr>
</tbody>
</table>

No. of patients

Gender (no. of patients)

- Male: 48
- Female: 5
- Other: 13

Risk factor

- Intravenous drug user: 40
- Other: 13

Phenotype

- Primary: 48
- Secondary: 5

Acetylator phenotype

- Fast: 20
- Slow: 33

Tobacco smokers: 42

Receiving Rifampin: 7

Receiving DDI: 17

Receiving AZT: 17

p24 antigen negative: 24

CD4⁺ lymphocyte (cells/μl): 25 (0–389)

ALT⁺ (IU/liter): 54 (23–508)

Bilirubin (mg/dl): 0.7 (0.3–8.0)

* Continuous covariates are indicated as mean (range).

ALT, alanine aminotransferase.

RESULTS

The number of concentrations in plasma available for analysis at each sampling time interval are depicted in Fig. 1. The decline in the concentration of dapsone following the oral administration of dapsone was best described by a one-compartment open model with first-order rate constants for absorption and elimination. The model was parameterized as the absorption rate constant (Ka), the apparent volume of distribution (V/F), and plasma clearance/bioavailability (CL/F), and plasma clearance/bioavailability (CL/F) by using the program-supplied routine ADVAN2 (32). Results of pharmacokinetic parameters were modeled with a constant coefficient of variation, while residual variability was found to be best described by a proportional-plus-constant-error model.

Several covariates were tested by addition to the basic model. Each covariate was considered significant if its addition to the model resulted in a reduction of the objective function by a factor greater than 3.8 (P < 0.05 compared with a chi-square distribution with 1 degree of freedom). Covariates were considered borderline and were not included in the final model if they reduced significantly the objective function but the null value was included within the 95% confidence interval. Plots of weighted residuals versus predicted concentrations were also used as additional help in model building. All significant covariates were included in a full model and were deleted one by one in order to reevaluate significance when other covariates were in the model. A covariate was not retained in the model if its deletion did not result in an increase in the objective.
The objective function when setting percentage for both parameters. This was done by comparing of rifampin on CL/F and V/F. After a final model for significant covariates was achieved, the models for inter- and intraindividual variabilities were retested. The variance of V/F decreased to a very small value and was no longer significant. The parameters obtained with the final model are reported in Table 3. The concentrations predicted by the final model versus the concentrations observed in plasma are plotted in Fig. 2.

**TABLE 2. Summary of model-building process: addition of covariates to the basic model (step 1) and deletion of covariates from the full model (step 2)**

<table>
<thead>
<tr>
<th>Step and covariate</th>
<th>Change in objective function, answera</th>
<th>CL/F</th>
<th>V/F</th>
<th>Ka</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>Wt</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>Ht</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>Body surface area</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>5.55, S</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>Acetylator phenotype</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>Tobacco smoker</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>Receiving rifampin</td>
<td>10.93, S</td>
<td>5.62, S</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>Receiving DDI</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>Receiving AZT</td>
<td>4.62, B</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>p24 antigen</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>CD4+ lymphocyte count</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td></td>
</tr>
<tr>
<td>ALT level</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>&lt;3.8, NS</td>
<td>5.00, S</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>&lt;3.8, NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>11.50, S</td>
<td>5.25, S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>4.22, S</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a S, significant; B, borderline; NS, not significant.

b ALT, alanine aminotransferase.

dation predicted by the final model versus the concentrations observed in plasma are plotted in Fig. 2.

**TABLE 3. Population pharmacokinetic parameters of dapsone administered to HIV-positive patients for PCP prophylaxis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\theta_1$ (liters/h)</th>
<th>$\theta_2$ (liters)</th>
<th>$\theta_3$ (h$^{-1}$)</th>
<th>$\theta_4$</th>
<th>CV CL/F (%)</th>
<th>CV Ka (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.83</td>
<td>69.6</td>
<td>0.696</td>
<td>-0.119</td>
<td>35</td>
<td>85</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>1.57, 2.09</td>
<td>57.4, 81.8</td>
<td>0.72, 1.36</td>
<td>0.318, 1.074</td>
<td>-0.08, -0.158</td>
<td>20, 46</td>
</tr>
</tbody>
</table>

a $\theta_1$, CL/F for patients not taking rifampin; $\theta_2$, V/F for patients not taking rifampin; $\theta_3$, $\theta_4$, and bilirubin (in milligrams per deciliter); $\theta_5$ (in hours $^{-1}$): $\theta_4$, increase of CL/F and V/F in patients taking rifampin, modeled as $\text{CL/F} = 0 + \theta_4 \times 0$ and $\text{V/F} = 0 + \theta_4 \times 0$; therefore, $\theta_5$ represents the percent increase in the values of the parameter with concomitant rifampin therapy, which is 69.6% for both CL/F and V/F; CV CL/F and CV Ka, interpatient variability of CL/F and Ka, respectively.

**DISCUSSION**

The disposition of dapsone has been reported by some investigators to be biexponential (11, 32). Dapsone may show a short distribution phase which was not evident in our data. Therefore, the data were best fitted with a monoeponential model, in agreement with some other reports (9, 12, 13).

The mean values (95% confidence intervals) of the pharmacokinetic parameters obtained with the basic model without covariates were 1.98 liters/h (1.65 to 2.31 liters/h) for CL/F, 75.2 liters (62.7 to 87.7 liters) for V/F, and 0.981 h$^{-1}$ (0.631 to 1.331 h$^{-1}$) for $\text{Ka}$. After the inclusion of covariates in the model, the variability for each parameter decreased appreciably from 43 to 35% for CL/F, from 19% to nonsignificant for V/F; and from 98 to 84% for $\text{Ka}$. The study of the effect of covariates on the pharmacokinetic parameters of dapsone was performed by using the population approach as a tool for pharmacokinetic screening; i.e., each covariate was tested for its effect on each pharmacokinetic parameter without any a priori selection of the covariates to undergo testing. For this reason we included in the analysis a few covariates which were not evenly represented in the population such as gender, treatment with rifampin, prophylaxis, and tobacco smoking. Our findings regarding such covariates should be confirmed by studies with larger numbers of patients.

Weight, height, body surface area, and stage of disease (CD4+ lymphocyte count, p24 antigen level, and primary versus secondary prophylaxis) did not have an influence on the pharmacokinetic parameters, in agreement with a previous report (11).

Study site, a marker for the formulation used, did not have a significant effect on the pharmacokinetic parameters.

As expected, acetylator phenotype did not have an effect on the pharmacokinetic parameters. This is because acetylation is not the rate-determining step in the elimination of dapsone and is not the only route of metabolism. It has been hypothesized that MADDs acts as an available pool for dapsone and that elimination of MADDs is mainly by reconversion to dapsone (32). The conversion of dapsone to other metabolites, such as N-hydroxylamine dapsone, which is associated with toxicity, will determine a reequilibration so that MADDs will be deacetylated to dapsone.

AZT appeared to decrease the clearance of dapsone by approximately 25%. However, this effect was considered borderline and was not included in the model. It may be interest-
ing to study this interaction in a study with a standard crossover design. Other borderline effects included a 28% increase in V/F in tobacco smokers and a 35% decrease of V/F in drug addicts compared with the value for patients with other risk factors. Gender significantly influenced the value of V/F in step 1 of the model building, with a 25% reduction of V/F for the female patients. However, the 95% confidence interval was broad and the effect was close to being considered borderline. In the model refinement step, gender was not retained in the model. It is possible that the small number of women included in this study account for the overall lack of significance of gender on V/F.

It has been suggested that rifampin increases the dapsone CL/F by inducing the activity of the hepatic microsomal enzyme P4503A4 (12, 32). However, the effect of rifampin on dapsone pharmacokinetics in the AIDS patient population has never been studied, to our knowledge. When the effect of rifampin on CL/F was modeled to be different from that on V/F (step 2 of the model building, as described in Table 2), rifampin appeared to result in a 112% increase in the CL/F and a 49.4% increase in the V/F of dapsone. Such a model would reflect the situation in which rifampin decreases F by enhancing the first-pass effect and increases metabolic clearance. Following the administration of rifampin, the value of CL/F would increase by a greater factor than the value of V/F since the change in CL/F would be caused by a change in both CL and F, while the modification in V/F would be due only to a decrease of F. In a further step, we tested the hypothesis that the effect of rifampin on the CL/F and V/F of dapsone could be proportionally the same. With this model rifampin resulted in an increase of 69.6% of the values of both CL/F and V/F.

Under this model, the effect of rifampin on the dapsone CL/F is mostly due to an effect on F, i.e., a first-pass effect, whereas the effect on metabolic clearance is small compared with the change in F. This may be true because elimination pathways involving the kidneys have been shown to compensate for changes in hepatic clearance (3, 12). Furthermore, it is known that the induction of the P4503A4 enzyme in the gut wall by rifampin plays an important role in decreasing the concentrations of certain orally administered drugs (2a). Thus, the increase in the first-pass effect in patients treated with rifampin may be quite high for dapsone, since the induction of metabolism by rifampin may affect the metabolism both in the liver and in the gut wall. We decided to use this as a final model because when the effect of rifampin on CL/F and V/F was modeled to be the same percentage for both CL/F and V/F, the objective function did not increase significantly and the model parameters were determined with slightly better precision.

However, this choice may be the subject of debate. It must be noted that the values of the dapsone pharmacokinetic parameters estimated by the two models did not differ appreciably. When the effect of rifampin on CL/F and V/F was modeled to be proportionally different, the mean values of CL/F, V/F, and half-life were 3.82 liters/h, 105.6 liters, and 19.2 h, respectively, while in the model that we considered final they were 3.10 liters/h, 118.0 liters, and 26.4 h, respectively. All the other population pharmacokinetic parameters were similar in both models.

A recent study with healthy volunteers (24) showed a substantially greater effect of rifampin on dapsone CL/F compared with the one found in our study with AIDS patients. Among healthy volunteers, the dapsone CL/F was 2.01 liters/h for subjects not taking rifampin concomitantly and 7.17 liters/h for subjects taking rifampin, with an increase of 257%. A formal crossover study is needed to elucidate whether rifampin induces the CL/F of dapsone in AIDS patients to a lesser extent than in healthy volunteers.

In the study mentioned above (24), it is also noteworthy that there was a major decrease in the MADDs area under the concentration-time curve (AUC), from 20.37 to 3.86 mg · h/liter, as a consequence of rifampin administration. Such a decrease was evident from our data, since for 5 of 7 patients taking rifampin MADDs was not detectable in plasma, while for only 2 of 46 patients not taking rifampin concomitantly, MADDs was not detectable in plasma. It has been the subject of debate whether HIV-positive patients have a different distribution of acetylation phenotypes as a consequence of factors such as concurrent infections, nutrition, liver disease, or concomitant drug administration. Two studies suggest that the slow acetylator phenotype appears to be significantly increased in the AIDS patient population (5, 20), assuming that in the healthy caucasian population the ratio of slow to fast acetylators is approximately 1:1 (10, 28). The authors of the works cited above (5, 20) hypothesize that such an increase may be clinically relevant in inducing a higher rate of cutaneous hypersensitivity to TMP-SMX, which is less metabolized by slow acetylators. However, another study comparing the distribution of slow to fast acetylators among HIV-positive patients and healthy volunteers in Canada failed to show a difference (30). We found 20 (37.7%) fast acetylators and 33 (62.3%) slow acetylators. Excluding the 7 patients treated with rifampin, our study population was represented by 19 (41.3%) fast acetylators and 27 (58.7%) slow acetylators. The prevalence of the slow acetylator phenotype in 19 healthy Italian volunteers was 79%, while that of the fast acetylator phenotype was 21%. Therefore, our study does not support the hypothesis of a higher prevalence of slow acetylators among HIV-positive patients. However, it seems possible that several factors, such as rifampin administration, may contribute to an alteration in the distribution of the acetylator phenotype among HIV-positive patients. It must be pointed out that if the hypothesis of a higher prevalence of slow acetylators in patients with HIV infection is true and that if the correlation between such a higher prevalence and the higher rate of severe side effects to TMP-SMX exists, a selection of slow acetylators in our study may have occurred since most of the patients were treated with dapsone because they could not tolerate the first-line combination of TMP-SMX for PCP prophylaxis. If this is the case, the general HIV-positive population would have a lower prevalence of slow acetylators than that observed in our study. This would strengthen our hypothesis contrasting a higher prevalence of slow acetylators among HIV-positive patients compared with that among healthy volunteers.

Increased alanine aminotransferase and total bilirubin levels...
did not correlate with CL/F. It has been reported that cirrhosis is not associated with a change in oral clearance of dapsone, while minor changes have been observed in terms of acetylation ratio and the recovery ratio of dapsone in urine (12).

Modeling for Ka was attempted because 58 concentrations in plasma were available 3 h or less following administration, which is a close approximation to the mean time reported in the literature for the observation of the peak concentration of dapsone in the plasma of HIV-positive patients (11). The total bilirubin level was found to decrease the absorption rate constant. Seven patients had total bilirubin levels above 1.2 mg/dl, which is considered the upper limit of the normal value. All these patients tested positive for hepatitis C virus antibody and showed some degree of liver dysfunction. A possible explanation may be that these patients with hepatocellular dysfunction have either associated gastrointestinal dysfunction, which is not unusual in patients with severe cirrhosis, or a lack of bile salts, which may result in a slower rate of solubility of dapsone and, consequently, an apparent slower rate of absorption. It is noteworthy that because of the high interpatient variability of Ka, this finding is irrelevant from a clinical standpoint. Graphical observation of post hoc Bayesian estimates of Ka (data not shown) indicates that the values of Ka for patients with total bilirubin levels were at the lower bound of the values found for patients with normal total bilirubin levels.

Simulations of the concentration-versus-time curves following the administration of 100 mg of dapsone biweekly at steady state are presented in Fig. 3. The curves represent the typical values of dapsone for patients taking or not taking rifampin concomitantly and their respective 95% prediction intervals. The prediction intervals were constructed to provide information on the expected range of concentrations experienced by the HIV-positive patient population. For this purpose, the population model was used to simulate individual steady-state concentration-versus-time profiles for 200 subjects taking rifampin concomitantly and 200 subjects not taking rifampin concomitantly. For each time point the range of the 2.5 and 97.5 percentiles was determined, and these ranges were then joined to form the prediction interval-versus-time profile. For the simulation a value of Ka equal to 0.957 h⁻¹ was used. This value corresponds to the model prediction for a patient with a total bilirubin level of 0.7 mg/dl, which is the median value for patients with bilirubin levels within the normal range in this study population. Figure 3 shows that in an average patient not taking rifampin the peak (C max) and minimum (C min) concentrations in plasma are 1.42 and 0.24 mg/liter, respectively, for the 72-h interval and 1.52 and 0.14 mg/liter, respectively, for the 96-h interval. For patients taking rifampin, C max and C min are 0.84 and 0.14 mg/liter, respectively, for the 72-h interval and 0.90 and 0.08 mg/liter, respectively, for the 96-h interval. The time to C max is approximately 3.7 h and the half-life is 26.4 h.

The model in which the effect of rifampin on the CL/F and V/F of dapsone was allowed to be proportionally different predicted essentially the same values for the mean C max and the mean time to C max compared with the values predicted by the model that was considered to be final, while C min was 0.075 mg/liter for the 72-h dosing interval and 0.033 mg/liter for the 96-h dosing interval.

It has been shown that a concentration of 0.1 mg/liter inhibits the growth of P. carinii in cell culture (8). It is not known whether the concentration of dapsone must remain above the MIC for the entire dosing interval in order to inhibit the replicative activity of P. carinii. In other words, it is not known whether the time above the MIC is the parameter of drug exposure which better predicts the efficacy of dapsone against P. carinii. TMP-SMX is highly effective against P. carinii, despite concentrations in plasma that are undetectable for prolonged periods of time between doses. This observation would suggest a postantibiotic effect on regrowth. If this is true for dapsone, parameters such as C max/MIC or AUC/MIC may be more predictive of the efficacy of dapsone. Furthermore, it is controversial whether the method used to determine the dapsone MIC in vitro is representative of the drug's in vivo efficacy. If time above the MIC is an important determinant of efficacy and if the MIC determined by in vitro assays is clinically relevant, our study suggests that twice-weekly administration of 100 mg of dapsone should be an appropriate dosage regimen for patients not taking rifampin, since levels in plasma remain above 0.1 mg/liter over the entire dosing interval for most of the patients. However, the percentage of patients with levels in plasma that temporarily fall below the MIC is higher among patients concomitantly treated with rifampin. Rifampin also results in a decrease in the dapsone C max and AUC, which could be of importance if C max/MIC or AUC/MIC are better predictors of efficacy. Whether the effect of rifampin on the plasma concentration-versus-time profile of dapsone is clinically relevant should be investigated.

In conclusion, the population pharmacokinetic parameters obtained in our study may be useful for dosage regimen optimization in the HIV-positive patient population. If time above the MIC predicts the efficacy of dapsone against P. carinii, the administration of 100 mg biweekly appears appropriate because it is associated with sustained levels in the plasma of most of the patients.

Among several covariates which were tested for their influence on pharmacokinetic parameters, concomitant administration of rifampin appeared to be the only significant factor capable of altering dapsone pharmacokinetics to an extent which could be clinically relevant. However, the effect of rifampin on the dapsone CL/F was less than expected. Our findings regarding the effect of rifampin on dapsone pharmacokinetics as well as the clinical relevance of such an interaction should be evaluated in a further study involving a larger number of patients.

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REFERENCES


