NOTES

Effects of Fluconazole and Clarithromycin on Rifabutin and 25-O-Desacetylrifabutin Pharmacokinetics

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Ten human immunodeficiency virus-infected patients were given rifabutin in addition to fluconazole and clarithromycin. There was a 76% increase in the area under the concentration-time curve of rifabutin when either fluconazole or clarithromycin was given alone and a 152% increase when both drugs were given together with rifabutin. Patients should be monitored for adverse effects of rifabutin administered concomitantly with clarithromycin and/or fluconazole.

The potential for drug interactions is high in human immunodeficiency virus (HIV)-infected patients treated with multiple medications. Rifabutin has been well documented to cause uveitis and arthralgias when high doses are prescribed or when high levels in plasma are attained (8). The objective of this study was to characterize the pharmacokinetics of rifabutin in the presence of fluconazole, clarithromycin, or both agents in combination.

Data were obtained from stored samples collected during an earlier study that evaluated the pharmacokinetics of stavudine in the presence of multiple medications for opportunistic infections (7). The study was an open-label, sequential, randomized trial that enrolled 10 HIV-infected patients with a CD4 count of less than 200 cells/mm³, who were at least 18 years old.

Differences in pharmacokinetic parameters of rifabutin and 25-O-desacetylrifabutin were determined by a two-way analysis of variance with SYSTAT, version 6.0 (SPSS Inc., Chicago, Ill.). Data were log transformed for statistical analysis. Post-hoc pairwise comparisons were performed using Tukey’s honestly significant difference test. A P value of <0.05 was considered significant.

Ten patients (9 male and 1 female), with an average age of 39 years (range, 30 to 49), were enrolled in and completed the study. The mean baseline CD4 cell count, percent CD4 cells, and viral load were 62 cells/mm³ (range, 9 to 143), 6% (range, 1 to 14), and 233,727 HIV RNA copies/ml (range, <10,000 to 608,000), respectively. No significant alterations were observed in hepatic or renal function during the study.

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TABLE 1. Pharmacokinetics of rifabutin in combination with clarithromycin and fluconazole

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>C_{max} (ng/ml)</th>
<th>C_{min} (ng/ml)</th>
<th>AUC_{0–24h} (ng · h/ml)</th>
<th>T_{max} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>244.9 ± 91</td>
<td>53.3 ± 49</td>
<td>3,109 ± 1,402</td>
<td>4.3 ± 1.8</td>
</tr>
<tr>
<td>R + F</td>
<td>468.6 ± 206</td>
<td>138.9 ± 101</td>
<td>5,463 ± 2,750</td>
<td>3.2 ± 1.4</td>
</tr>
<tr>
<td>R + C</td>
<td>452.2 ± 201</td>
<td>140.6 ± 82</td>
<td>5,476 ± 2,852</td>
<td>3.6 ± 2.1</td>
</tr>
<tr>
<td>R + F + C</td>
<td>609.5 ± 284</td>
<td>214.8 ± 146</td>
<td>7,852 ± 3,907</td>
<td>4.0 ± 1.9</td>
</tr>
</tbody>
</table>

a R, rifabutin; F, fluconazole; C, clarithromycin.

Since rifabutin is usually dosed as a once-daily regimen, our 8-h sampling would not yield concentrations that are reflective of levels in plasma for the entire dosing interval. A Bayesian approach was applied to simulate a 24-h dosing interval, using a model with parameters for rifabutin from a previous study. Using this model and the previous data (6) as Bayesian priors, we could achieve excellent fits of our data and accurately estimate a 24-h AUC. Rifabutin disposition was well described by a two-compartment model with a lag time for absorption. We could achieve excellent fits of our data and accurately estimate a 24-h AUC. Rifabutin disposition was well described by a two-compartment model with a lag time for absorption. We could achieve excellent fits of our data and accurately estimate a 24-h AUC. Rifabutin disposition was well described by a two-compartment model with a lag time for absorption. We could achieve excellent fits of our data and accurately estimate a 24-h AUC. 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