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Pharmacokinetic Study of Tenofovir Disoproxil Fumarate Combined with Rifampin in Healthy Volunteers


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Tenofovir disoproxil fumarate (tenofovir DF) was studied in combination with rifampin in 24 healthy subjects in a multiple-dose, open-label, single-group, two-period study. All subjects were given tenofovir DF at 300 mg once a day (QD) from days 1 to 10 (period 1). From days 11 to 20 the subjects received tenofovir DF at 300 mg combined with rifampin at 600 mg QD (period 2). The multiple-dose pharmacokinetics of tenofovir (day 10 and 20) and rifampin (day 20) were assessed. The drug-related adverse events (AEs) experienced during this study were mostly mild. Only one grade 3 AE possibly or probably related to the treatment (raised liver enzyme levels) occurred during period 2; the subject was withdrawn from the study. Pharmacokinetic data for 23 subjects were thus evaluable. Point estimates for the mean ratios of tenofovir with rifampin versus tenofovir alone for the area under the concentration-time curve from time zero to 24 h (AUC0-24), the maximum concentration of drug in plasma (Cmax), and the minimum concentration of drug in plasma (Cmin) were 0.88, 0.84, and 0.85, respectively. The 90% classical confidence intervals for AUC0-24, Cmax, and Cmin were 0.84 to 0.92, 0.78 to 0.90, and 0.80 to 0.91, respectively, thus suggesting pharmacokinetic equivalence. Similarly, coadministration of rifampin and tenofovir DF did not result in changes in the values of the tenofovir pharmacokinetic parameters. For rifampin, the values of the pharmacokinetic parameters found in this study were comparable to those found in the literature, indicating that tenofovir DF has no effect on the pharmacokinetics of rifampin. In conclusion, adaptation of either the rifampin or the tenofovir DF dose for the simultaneous treatment of tuberculosis and human immunodeficiency virus (HIV) infection in HIV-infected patients is probably not required.

Coinfection with Mycobacterium tuberculosis and human immunodeficiency virus (HIV) is frequent, particularly in Africa and Asia (3, 14, 18). Simultaneous treatment of tuberculosis and HIV infection may lead to complex combination therapy. Rifampin is a drug of choice for the treatment of tuberculosis. Rifampin is known to have major pharmacokinetic interactions with HIV protease inhibitors and nonnucleoside reverse transcriptase inhibitors (8, 10, 12, 13, 16, 17). Tenofovir disoproxil fumarate (tenofovir DF) is the first drug from a new class of anti-HIV agents (nucleotide reverse transcriptase inhibitors) that has been recently approved for use for the treatment of HIV infections in adults. However, no data are available regarding its pharmacokinetics in combination with tuberculosis drugs, in particular, rifampin. No influence of rifampin on the pharmacokinetics of tenofovir is expected, because both drugs are metabolized and eliminated in different ways. Tenofovir is eliminated unchanged by glomerular filtration and active tubular secretion (1, 6), while rifampin is extensively metabolized by intestinal and hepatic metabolism (4). However, a pharmacokinetic interaction cannot be excluded.

The clinical trial described here was designed to explore the pharmacokinetics of tenofovir DF with and without rifampin in an effort to establish whether there is a need to adjust the dosage of either medication when the two medications are used for the treatment of patients coinfected with M. tuberculosis and HIV.

MATERIALS AND METHODS

Study design. The present study was designed to evaluate the effect of 600 mg of rifampin on the pharmacokinetics of 300 mg of tenofovir DF and also to assess whether tenofovir DF has a substantial impact on steady-state exposure to rifampin. This study was a multiple-dose, open-label, single-group, two-period study with 24 healthy volunteers. First, the subjects received tenofovir DF at 300 mg once daily (QD) for 10 days (period 1). At study day 10, a steady-state 24-h pharmacokinetic curve was obtained for tenofovir. During the second period of the study (period 2), tenofovir DF at 300 mg was combined with rifampin at 600 mg QD, again for 10 days. At study day 20, 24-h steady-state pharmacokinetic curves were obtained for tenofovir and rifampin. During the study both tenofovir DF and rifampin had to be taken with breakfast. On the days prior to study days 9 and 19, the subjects reported to the study center for direct observation of dosing with the medications with a standardized breakfast. Subsequently, on the evenings of study days 9 and 19 the subjects remained at the study center for two overnight stays and remained at the study center until the mornings of study days 11 and 21, respectively. On days 9, 10, 11, 19, and 20 the subjects received a standardized breakfast of 550 kcal (two slices of white bread, 15 g of low-fat margarine, 14 g of jelly, 150 ml of orange juice, and 150 ml of skim milk). The medication was administered immediately after breakfast with 200 ml of tap water. All other meals and snacks on the pharmacokinetic study days were also standardized. When the subjects took the medication at home, study drugs were administered with breakfast (at least two and at most three slices of wheat bread).

No crossover design was used in this study because rifampin could lead to considerable carryover effects, due to its long-lasting cytochrome P450-inducing effect. To eliminate this effect a longer washout period would be necessary, but this would have significantly prolonged the duration of the study and would have...
led to difficulties with subject recruitment and retention. This study was reviewed and approved by the independent ethics committee Arnhem-Nijmegen. Written informed consent was obtained from each study subject prior to the conduct of any study-related activity.

**Study subjects.** Twenty-four healthy male and female subjects were eligible for inclusion in the study. The subjects could be between 18 and 65 years of age with a body weight of at least 50 kg and in good age-appropriate health condition, as established by the individual’s medical history; a physical examination; electrocardiography; and the results of biochemistry, hematology, and urine analyses within the 3 weeks prior to administration of the first dose. Other inclusion criteria were an ability to sign informed consent voluntarily and a willingness to refrain from the use of contact lenses during the treatment with rifampin. Exclusion criteria were as follows: positive tests for HIV, hepatitis B virus, or hepatitis C virus; a tuberculin skin test reaction of more than 15 mm in diameter with a negative response to the Mantoux test or a positive result on the tuberculin skin test with a skin reaction of more than 15 mm in diameter; pregnancy; breast-feeding; a history of alcohol or drug abuse within 6 months prior to the study; and the use of any medication that could interfere with the pharmacokinetics of the test drugs.

**Safety.** Blood samples for serum biochemistry analyses, including tests for glucose and hematologic analyses, and urine samples for urinalysis were taken on study days 1, 4, 9, 11, 15, 19, and 21. These samples were taken while the subjects were in a fasting condition. In females of childbearing potential, testing of blood samples for human chorionic gonadotropin was performed at the screening visit and on study days 1, 9, and 19 with the Instacheck Multi-Drug Screen panel (Frontire Diagnostics, San Diego, Calif.). Vital signs for cardiovascular safety (systolic and diastolic blood pressures and heart rate) were monitored, and an electrocardiogram was recorded at the screening visit. The medical and nursing staff of the trial center monitored the subjects for adverse events (AEs) throughout their confinement. Subjects voluntarily reported any AE or reported AEs in study days 1, 9, and 19 with the Instacheck Multi-Drug Screen panel (Frontire Diagnostics, San Diego, Calif.). Vital signs for cardiovascular safety (systolic and diastolic blood pressures and heart rate) were monitored, and an electrocardiogram was recorded at the screening visit. The medical and nursing staff of the trial center monitored the subjects for adverse events (AEs) throughout their confinement. Subjects voluntarily reported any AE or reported AEs in response to general questioning. All AEs occurring between the first intake of the trial medication(s) and the end of the trial were reported. The relationship of the trial drug(s) was not related or unlikely to be related to the trial drug(s) if evidence existed that the AE had a source other than the trial drug(s). AEs were recorded as possibly or probably related to the trial drug(s) if a temporal relationship existed between the event onset and administration of the trial drug(s) and there was no evidence of an alternative cause for the event.

The severities of the AEs were recorded and graded according to the common toxicity criteria (grades 1, 2, 3, and 4) of the National Institute of Allergy and Infectious Diseases.

**Bioanalysis.** Tenofovir concentrations were determined by using a validated high-performance liquid chromatography assay with a fluorometric detector by a previously described (12) bioanalysis. Tenofovir concentrations were determined by using a validated high-performance liquid chromatography method. The concentrations of the quality controls used were 2.85, 9.5, and 24 mg/liter. The intra- and interassay coefficients of variation were less than 11% for all quality controls. The lower limit of quantification was 0.0045 mg/liter. The rate of recovery of tenofovir from human plasma was 86%.

Rifampin concentrations were determined by using a previously described (12) high-performance liquid chromatography method. The concentrations of the quality controls used were 2.85, 9.5, and 24 mg/liter. The intra- and interassay coefficients of variation were less than 1% for all quality controls. The lower limit of quantification was 0.0045 mg/liter.
0.85 (0.80 to 0.91) for AUC0-24, Cmax, and Cmin, respectively, suggesting pharmacokinetic equivalence when tenofovir DF was dosed with or without rifampin.

Figure 1 illustrates the effects of rifampin on the mean concentration-time profiles of tenofovir. Table 2 presents the values of the pharmacokinetic parameters for rifampin when it was combined with tenofovir and the values of the pharmacokinetic parameters of rifampin from the literature (4, 15). The values of the pharmacokinetic parameters for rifampin when it was combined with tenofovir are comparable to those in the literature when rifampin is administered with food, suggesting that tenofovir has no influence on rifampin exposure.

Safety. All 24 subjects reported one or more AEs at some time during the study. No subject experienced a grade 4 AE or a serious AE. In total, 160 grade 1 or grade 2 AEs were reported. A total of 102 AEs were judged to be possibly or probably related to a study drug(s). During treatment with tenofovir DF (period 1), 33 possibly or probably related AEs were reported, while during period 2 (tenofovir DF combined with rifampin), 69 possibly or probably related AEs were reported. Of the 69 AEs reported during period 2, 24 AEs were related only to rifampin. Each subject reported discoloration of the urine. Most of the study drug-related AEs were mild (85% were grade 1 in severity). All AEs resolved after the withdrawal of treatment.

All 24 subjects completed treatment period 1 (tenofovir DF alone). The most common AEs that were reported during treatment with tenofovir DF were fatigue, headache, and gastrointestinal disorders.

During period 2 one subject was withdrawn from the study due to several complaints, which were rash, headaches, abdominal disorders, fatigue, somnolence, and dizziness. The study medications were stopped on study day 15. At the follow-up visit, 5 days later, the subject developed elevated liver enzyme levels, which were judged to be a grade 3 AE. Nine days after the first follow-up visit the liver enzyme levels returned to normal. The AEs that occurred during the combination treatment with tenofovir DF and rifampin consisted mainly of flu-like symptoms (e.g., fatigue, headache, and gastrointestinal disorders) and urine discoloration, which are well-known AEs of rifampin (7).

No clinically significant hematology or urinalysis values were observed in this study.

DISCUSSION

This study was designed to investigate whether rifampin influences the pharmacokinetics of tenofovir. The study showed that bioequivalence could be suggested for tenofovir DF combined with rifampin and tenofovir DF given alone and that the combination of tenofovir DF with rifampin was generally well tolerated, as only one patient prematurely discontinued from study.

The confidence intervals for AUC and Cmin were 0.84 to 0.92 and 0.80 to 0.91, respectively, while the confidence interval was

### Table 1. Pharmacokinetics of tenofovir

<table>
<thead>
<tr>
<th>Study day and</th>
<th>AUC0-24 (mg · h/liter)</th>
<th>Cmax (mg/liter)</th>
<th>Cmin (mg/liter)</th>
<th>Tmax (h)</th>
<th>t1/2 (h)</th>
<th>CL/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 10</td>
<td>3.56 ± 0.77 (3.48)</td>
<td>0.36 ± 0.080 (0.36)</td>
<td>0.071 ± 0.016 (0.069)</td>
<td>1.0 (1.0–3.0)</td>
<td>13.8 ± 4.53 (13.2)</td>
<td>88.1 ± 19.0 (86.2)</td>
</tr>
<tr>
<td>Day 20</td>
<td>3.11 ± 0.57 (3.06)</td>
<td>0.30 ± 0.060 (0.30)</td>
<td>0.060 ± 0.011 (0.059)</td>
<td>1.0 (1.0–2.0)</td>
<td>11.6 ± 2.77 (11.2)</td>
<td>99.8 ± 20.3 (98.0)</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>0.88 (0.84–0.92)</td>
<td>0.84 (0.78–0.90)</td>
<td>0.85 (0.80–0.91)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* a n = 23. CI, confidence interval.
* b Values are arithmetic means ± standard deviations (geometric means), unless indicated otherwise.
* c Values are medians (ranges).

### Table 2. Pharmacokinetics of rifampin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value on day 20 (this study)</th>
<th>Value in the literature (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (h)</td>
<td>2.4 (0.6)b</td>
<td>4.43 (1.11)</td>
</tr>
<tr>
<td>Cmax (mg/liter)</td>
<td>10.9 (3.0)</td>
<td>7.27 (2.25)</td>
</tr>
<tr>
<td>AUC0-12 (mg · h/liter)</td>
<td>43.27 (15.28)</td>
<td>50.97 (14.27)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1.5 (0.3)</td>
<td></td>
</tr>
</tbody>
</table>

* a The data are from reference 15 and are for subjects who received rifampin with breakfast.
* b Values are means (standard deviations).
addition of rifampin to tenofovir DF is well tolerated, and the small decrease in plasma tenofovir levels during combination treatment suggests that these drugs can be coadministered without the need for dose adjustments. This implies that standard doses should be a starting point for the use of these medications by HIV-infected patients. Additional pharmacokinetic studies in a clinical setting are warranted to confirm the findings of this study.

ACKNOWLEDGMENTS

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