Rifampicin Reduces Plasma Concentrations of Moxifloxacin in Patients with Tuberculosis

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Background. The long duration of the current tuberculosis (TB) treatment is demanding and warrants the development of new drugs. Moxifloxacin shows promising results and may be combined with rifampicin to shorten the duration of TB treatment. Rifampicin induces the phase II metabolic enzymes that are involved in the biotransformation of moxifloxacin. Therefore, the interaction between rifampicin and moxifloxacin should be investigated.

Patients and methods. Nineteen Indonesian patients with pulmonary TB who were in the last month of their TB treatment completed a 1-arm, 2-period, fixed-order pharmacokinetic study. In phase 1 of the study, they received 400 mg of moxifloxacin every day for 5 days in addition to 450 mg of rifampicin and 600 mg of isoniazid 3 times per week. In phase 2 of the study, after a 1-month washout period, patients received moxifloxacin for another 5 days (without rifampicin and isoniazid). A 24-h pharmacokinetic curve for moxifloxacin was recorded on the last day of both study periods, and its pharmacokinetic parameters were evaluated for an interaction with rifampicin, using a bioequivalence approach.

Results. Coadministration of moxifloxacin with rifampicin and isoniazid resulted in an almost uniform decrease in moxifloxacin exposure (in 18 of 19 patients). The geometric means for the ratio of phase 1 area under the curve to phase 2 area under the curve and for the ratio of phase 1 peak plasma concentration to phase 2 peak plasma concentration were 0.69 (90% confidence interval, 0.65–0.74) and 0.68 (90% confidence interval, 0.64–0.73), respectively. The median time to reach peak plasma concentration for moxifloxacin was prolonged from 1 h to 2.5 h when combined with rifampicin and isoniazid (P < 0.003).

Conclusions. Coadministration of moxifloxacin with intermittently administered rifampicin and isoniazid results in reduced moxifloxacin plasma concentrations, which is most likely the result of induced glucuronidation or sulphation by rifampicin. Further studies are warranted to evaluate the impact of the interaction on the outcome of TB treatment.

Worldwide, tuberculosis (TB) causes ~2 million deaths each year [1, 2]. The main problem with TB treatment is its long duration (6 months), which is very demanding in terms of adherence and tolerability. New TB drugs may help to shorten the treatment duration. Following a study involving the quinolone ofloxacin [3], the quinolone antibiotics have raised great interest because of the possibility that their use will decrease the duration of TB treatment.

Newer-generation quinolones possess even greater in vitro activity against Mycobacterium tuberculosis than ofloxacin. The quinolone moxifloxacin, currently recommended for the treatment of multidrug-resistant TB [4], shows the highest in vitro activity against M. tuberculosis [5]. Moxifloxacin has shown the potential to shorten TB treatment by 2 months when used as a substitute for isoniazid in a murine model [6, 7]. Studies involving humans show that the early bactericidal activity of moxifloxacin is comparable to that of isoniazid [8, 9]. Furthermore, it has been shown that moxifloxacin is safe for long-term use in patients with TB [10]. A recent study evaluated the effect of moxifloxacin versus ethambutol (both administered in combination
with other TB drugs) on sputum conversion at 2 months [11], and similar studies are underway.

Rifampicin is the strongest known inducer of cytochrome P450 isoenzymes. No pharmacokinetic interaction between moxifloxacin and rifampicin is anticipated at the level of phase I metabolism, because moxifloxacin is entirely metabolized by the phase II metabolizing processes of glucuronidation and sulphation. However, rifampicin also induces the phase II enzymes uridine diphosphate glucuronosyltransferase and sulphotransferase, which may possibly affect the area under the curve (AUC) and peak plasma concentrations \( \text{C}_{\text{max}} \) of moxifloxacin. This interaction could also be of relevance in developed countries when moxifloxacin and rifampicin are combined in TB treatment (for example, for treatment of patients who are intolerant of first-line TB drugs or who have extensive TB that is isoniazid monoresistant [12]). The objective of this pharmacokinetic study was to assess the interaction between rifampicin and moxifloxacin.

**PATIENTS AND METHODS**

**Subjects.** Study subjects were Indonesian patients with pulmonary TB who were in the last month of the continuation phase of TB treatment. All study subjects had a body weight >35 kg, were 18–55 years of age, and had normal electrocardiogram findings. All patients had a satisfactory response to treatment, and none had sputum smear results positive for TB after 2 months of treatment. Subjects were excluded from the study if they were pregnant or lactating; had a relevant history or condition that might interfere with drug absorption, distribution, metabolism, or excretion; had heart rhythm disturbances; had a history of seizures or epilepsy; had a glucose 6 phosphate dehydrogenase deficiency; had hypersensitivity to quinolones; had experienced tendon disorders related to fluoroquinolone treatment; had hypokalemia; or had use of any drug that might interact with moxifloxacin.

**Study design.** This study was an open-label, multiple-dose, 1-arm, 2-period, fixed-order pharmacokinetic interaction study and was performed in an outpatient clinic in Bandung, Indonesia. According to the National Tuberculosis Program of Indonesia, the continuation phase of TB treatment consists of 600 mg of isoniazid and 450 mg of rifampicin, both administered 3 times per week. The dose of rifampicin is lower than the usual 600-mg dose because of the low mean body weight of Indonesian people. Because all patients were in the last month of TB treatment, steady state for rifampicin and isoniazid was already achieved at the start of the study. In addition to regular TB treatment, subjects were given 400 mg of moxifloxacin every day for 5 days to attain steady state of this drug (figure 1) [13]. After completion of TB treatment and a washout period of 1 month, patients received 400 mg of moxifloxacin per day for another 5 days. A full pharmacokinetic curve was recorded at day 5 in both phases of the study. Intake of study medication was observed on days 1, 3, and 5 in each phase. Furthermore, adherence to study medication was evaluated by counting capsules and by the use of Medication Event Monitoring System vials. These vials contain microprocessors that register the date and time of each opening of the vial. All patients gave written informed consent, and both the Ethical Review Board of Hasan Sadikin Hospital, Padjadjaran University (Bandung, Indonesia), and the Advisory Board of Radboud University Nijmegen Medical Centre (Nijmegen, The Netherlands) approved the study.

**Experimental procedures.** Steady state pharmacokinetic parameters were assessed on the last day in both phases. Patients were asked to refrain from any food intake from 11 pm the preceding night until standardized lunch was provided, 4 h after intake of study medication. Study drugs (moxifloxacin in phase 1 and phase 2, plus rifampicin and isoniazid in phase 1 only) were taken together on an empty stomach. To assess plasma concentrations of moxifloxacin and rifampicin, serial blood sampling was performed before intake and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h after intake of the drugs. All blood samples were centrifuged immediately and frozen at −20°C within 20 min after collection. Afterwards, all samples

![Figure 1](http://cid.oxfordjournals.org/)

**Figure 1.** Study design, showing dosing schedules for phase 1 and phase 2 of the study. The washout phase had a duration of 1 month. Phase 1 took place in the last month of tuberculosis treatment; therefore, steady state was already achieved for rifampicin and isoniazid at the start of the study. Phase 2 took place 1 month after the end of tuberculosis treatment. INH, isoniazid (600 mg administered 3 times per week); MXF, moxifloxacin (400 mg administered once daily); PFK, pharmacokinetic assessment; Rif, rifampicin (450 mg administered 3 times per week); S, screening.
were transferred to −80°C. Samples were shipped on dry ice to The Netherlands for bioanalysis.

**Plasma concentrations.** Moxifloxacin plasma concentrations were measured by means of a validated high-performance liquid chromatography method with fluorescence detection. Accuracy was >95% for the moxifloxacin standard concentrations of 0.074 mg/L, 0.15 mg/L, 0.74 mg/L, and 7.4 mg/L. Intraday precision and between-day precision (expressed as coefficient of variation) ranged from 1.4% to 5.4% and from 0.2% to 3.9%, dependent on the concentration. Ninety-eight drugs were tested for interference. The lower and upper limits of quantitation were 0.03 mg/L and 10.0 mg/L, respectively. Moxifloxacin in plasma is stable at −20°C and −80°C for at least 12 months. The plasma concentrations of rifampicin and desacetyl rifampicin were analyzed by a previously described validated high-performance liquid chromatography UV method [14]. Accuracy was 99.8%, 100.4%, and 100.4% for the rifampicin standard concentrations of 2.9 mg/L, 9.5 mg/L, and 23.7 mg/L, respectively. The accuracy of the desacetyl rifampicin standard concentrations of 0.09 mg/L, 2.25 mg/L, and 27.0 mg/L was 103.9%, 102.4%, and 102.6%, respectively. Intraday precision and between-day precision ranged from 0.7% to 1.1% and from 0.1% to 0.6%, respectively, for rifampicin and from 0.9% to 2.9% and from 0.5 to 3.6%, respectively, for desacetyl rifampicin. Rifampicin in plasma is stable for at least 16 months at −20°C and −80°C. Concentrations of isoniazid were not assessed, because measurement of this drug was not relevant to the study.

**Tolerability and safety.** Tolerability and safety were assessed on days 1, 3, and 5 in both study phases. Patients were actively questioned about the occurrence of the known adverse effects of moxifloxacin. Clinical chemistry and hematological tests and evaluations of vital signs (i.e., heart rate and blood pressure) and electrocardiograms were performed on the same days. All possible adverse events were graded according to the Common Toxicity Criteria, version 2.0 [15].

**Pharmacokinetic and statistical analysis.** All pharmacokinetic evaluations for rifampicin and moxifloxacin were performed using noncompartmental methods with WinNonLin software, version 4.1 (Pharsight). The highest observed plasma concentration was defined as Cmax, with the corresponding time as tmax. Cmin was the plasma concentration at 24 h after intake of study medication. The AUC0–24h was calculated using the log-linear trapezoidal rule from 0 to up to the last concentration. The terminal log-linear period (log C vs. t) was based on the last data points (n ≥ 3). The absolute value of the slope was calculated by least-squares linear regression analysis. β is the first-order elimination rate constant. Terminal half-life was obtained by the equation 0.693/β. The apparent clearance of the drug (Cl/F) was calculated by the formula dose/AUC0–24h. The volume of distribution (V/F) was calculated by the equation Cl/F/β.

The sample size of the study was derived from the main pharmacokinetic parameter, the AUC0–24h of moxifloxacin, and was determined for a data analysis that is similar to a within-subject 2-period bioequivalence study [16], as recommended for interaction studies. The desired power of the study was 90%, and the within-subject coefficient of variation for the logarithmically transformed AUC0–24h of moxifloxacin was conservatively estimated to be 15%. On the basis of these data, at least 12 subjects were required. Because this was an estimation and dropouts were expected, 22 patients were enrolled in the study.

The MIC of moxifloxacin for *M. tuberculosis* (0.5 mg/L [17])

### Table 1. Steady state pharmacokinetic results for moxifloxacin in a cohort of 19 patients.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric mean value (range)</th>
<th>Geometric mean ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0–24h, mg × h/L</td>
<td>33.3 (25.1–55.5)</td>
<td>48.2 (37.2–60.5)</td>
</tr>
<tr>
<td>Cmax, mg/L</td>
<td>3.2 (2.5–4.5)</td>
<td>4.7 (3.4–6.0)</td>
</tr>
<tr>
<td>Cmin, mg/L</td>
<td>0.38 (0.18–0.78)</td>
<td>0.78 (0.51–1.1)</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>2.5 (0.5–6.0)</td>
<td>1.00 (0.5–3.0)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>12.0 (7.2–16.0)</td>
<td>8.3 (6.6–10.8)</td>
</tr>
<tr>
<td>V/F, L</td>
<td>123 (83–187)</td>
<td>119 (84–179)</td>
</tr>
<tr>
<td>t1/2, h</td>
<td>7.1 (5.0–9.6)</td>
<td>9.9 (7.4–14.0)</td>
</tr>
</tbody>
</table>

**NOTE.** AUC0–24h, 24-h area under the concentration-time curve; Cmax, highest observed plasma concentration; Cmin, trough plasma concentration at 24 h after intake of study medication; CL/F, total clearance; F, bioavailability; tmax, time at which Cmax occurs; t1/2, elimination half-life; V/F, volume of distribution.

a Phase 1 therapy consisted of a combination of 400 mg of moxifloxacin administered once daily and 600 mg of isoniazid and 450 mg of rifampicin administered 3 times weekly.

b Phase 2 therapy consisted of 400 mg of moxifloxacin administered once daily.
c Median and range.
d By Wilcoxon signed-rank test.
Figure 2. Steady state 24-h area under the curve (AUC$_{0-24}$) of moxifloxacin when administered once daily (phase 2) and when combined with administration of rifampicin and isoniazid 3 times per week (phase 1) in a cohort of 19 patients.

was used to calculate the pharmacodynamic parameters AUC$_{0-24}$:MIC and C$_{max}$:MIC. The number of patients who reached the targets of AUC$_{0-24}$:MIC and C$_{max}$:MIC ratios of 100 and 10, respectively [18–23], was compared using the $\chi^2$ test. The mutant prevention concentration (MPC) for moxifloxacin in TB treatment was set at 2.5 mg/L [24], uncorrected for protein binding. Time greater than MPC was the time during which the moxifloxacin concentration was above the MPC.

All statistical evaluations were performed with SPSS for Windows, version 12.0.1 (SPSS). Pharmacokinetic parameters were log-transformed before statistical analysis. The values for $t_{max}$ were not transformed and were compared using the Wilcoxon signed-rank test. Using a bioequivalence approach for the evaluation of the interaction, the 90% CI of the geometric mean ratios AUC$_{phase 1}$:AUC$_{phase 2}$ of moxifloxacin was 0.69 (90% CI, 0.65–0.74). Similar figures were shown for moxifloxacin C$_{max}$ (table 1). Moxifloxacin C$_{min}$ showed a stronger decrease (geometric mean ratio, 0.38) when coadministered with rifampicin and isoniazid. As a result, bioequivalence for the combination of rifampicin, isoniazid, and moxifloxacin, compared with moxifloxacin alone, cannot be concluded. Moxifloxacin exposure decreased in all but 1 subject (figure 2). Moxifloxacin $t_{max}$ was prolonged when combined with rifampicin and isoniazid ($P < .003$; figure 3). A relatively small interindividual variability in pharmacokinetic parameters for moxifloxacin was observed, which has been described elsewhere [25].

The $AUC_{24\ h}$ for moxifloxacin without rifampicin (in phase 2) did not correlate with the relative difference between the 2 phases (i.e., AUC$_{phase 2}$:AUC$_{phase 1}$; Pearson correlation coefficient, 0.195; $P = .423$).

The geometric mean values for AUC$_{0-24\ h}$:MIC and C$_{max}$:MIC for moxifloxacin in phase 2 approached the desired values for fast growing bacilli (geometric mean values, 96.4 [range, 74.4–121] and 9.5 [range, 6.8–12.1], respectively), in contrast with the values in phase 1 (geometric mean values, 66.7 [range, 50.3–111] and 6.5 [4.9–9.1], respectively; $P < .01$). When moxifloxacin was given alone (in phase 2), 9 (47%) of 19 participants reached an AUC$_{0-24\ h}$:MIC that was $>100$, compared with only 1 patient (5%) when moxifloxacin was combined with rifampicin and isoniazid in phase 1. Results were similar with respect...
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Figure 3. Mean (± SD) moxifloxacin steady state plasma concentrations versus time (19 patients). Open squares indicate data for patients receiving 400 mg of moxifloxacin administered once daily. Closed squares indicate data for patients receiving a combination of 400 mg of moxifloxacin administered once daily and 450 mg of rifampicin and 600 mg of isoniazid administered 3 times per week. Bars indicate standard deviation.

to the C\text{max}:MIC ratio. The median time during which the moxifloxacin concentration was greater than the MPC was 5.5 h (range, 2.5–7.5 h) when given alone in phase 2, compared with 2 h (range, 0–7.5 h) when combined with rifampicin and isoniazid (P<.01).

The pharmacokinetic parameters of rifampicin and its main metabolite (desacetylrifampicin) are shown in table 2. No significant correlation was found between exposure to rifampicin (AUC\text{phase 1}) and the ratio of AUC\text{phase 1}:AUC\text{phase 2} for moxifloxacin (Pearson correlation coefficient, 0.168; P = .493). The 1 diabetic patient showed average exposure to rifampicin, although plasma rifampicin concentrations have been found to be reduced in patients with type 2 diabetes [26]. The patients experienced only grade I adverse events, and no laboratory abnormalities were detected.

DISCUSSION

To our knowledge, this report presents the first pharmacokinetic data regarding the use of moxifloxacin to treat patients with TB. Our study demonstrates that steady state plasma concentrations of moxifloxacin are significantly reduced when moxifloxacin is combined with rifampicin and isoniazid.

The interaction is expected to result from an increase in phase II metabolism caused by rifampicin, because moxifloxacin does not undergo phase I oxidative metabolism [13]. No interference of isoniazid in the metabolism of moxifloxacin is anticipated, because isoniazid is only known to affect cytochrome P450–mediated metabolism [27]. Rifampicin is known to be a very strong inducer of CYP-P450 isoenzymes. It is probably less well known that this drug also induces phase II metabolism. More specifically, rifampicin induces uridine diphosphate glucuronosyltransferase and sulphotransferase, thereby reducing plasma concentrations of rofecoxib, mycophenolate mofetil, lamotrigine, zidovudine, and propafenone [13, 28–34]. A similar mechanism may be involved in the interaction with moxifloxacin, because this drug undergoes phase II biotransformation and will be excreted as a sulpho-compound or as glucuronide via the kidneys (2.5% and 14%, respectively) and the feces (34% and 14%, respectively) [35]. Recently, it was found that, in healthy volunteers, rifampicin mainly induces the sulphation pathway of moxifloxacin [36]. Of note, the difference in t\text{max} between phases could be suggestive for a role of P-glycoprotein. The expression of P-glycoprotein in intestinal cells is induced by rifampicin, and moxifloxacin could be a substrate of this protein [37]. However, induced sulphation or glucuronidation could also cause this difference.

The AUC\text{0–24h} and C\text{max} of moxifloxacin showed mean decreases of 31% and 32%, respectively. This reduction in plasma concentrations can be characterized as modest, and similar reductions in AUC (27%) and t\text{max} were found in a similar study involving healthy subjects [36]. Strikingly, C\text{max} was found to be unaffected by rifampicin in this study [36]. In the current study, the reduction of moxifloxacin plasma concentrations occurred almost uniformly, in all but 1 of the study subjects. Daily dosing of rifampicin instead of intermittent dosing could possibly amplify the extent of this interaction. For gram-neg-
For M. tuberculosis, ifloxacin against activity are less well defined [21]. Recently, the activity of moxifloxacin when combined with rifampicin or other rifamycins has been found to be best described by the ratio between AUC and MIC [17, 20]. Nuernberger and Grosset [21] showed that even the potent quinolone moxifloxacin, when used in TB treatment, does not reach the ideal pharmacodynamic values for activity against gram-negative bacilli. Apart from this, an MPC has been defined [24], above which plasma concentrations should be maintained to prevent the emergence of resistance. It has been demonstrated that only a few quinolones (moxifloxacin among them) achieve brief periods of concentrations above the MPC [24]. In line with this, previous research using an aerosol model concluded that a moxifloxacin dosage of 800 mg per day (instead of 400 mg per day) is likely to achieve excellent antimicrobial activity against M. tuberculosis and suppress drug resistance [38]. It should be acknowledged that the clinical relevance of these pharmacodynamic parameters in patients receiving multidrug treatment of TB remains unclear. Presumably, the same interaction between rifampicin and moxifloxacin is occurring in the murine model of TB treatment, and even so, the substitution of moxifloxacin for isoniazid markedly improves the activity of treatment. Therefore, it should be concluded that the clinical relevance of the interaction between rifampicin and moxifloxacin is unknown at this time, and this applies to the administration of this drug combination to shorten the duration of TB treatment, as well as for other clinical situations in which this combination is used.

On the basis of the current study, we would propose that follow-up pharmacokinetic studies be performed to assess whether an increase in the dose of moxifloxacin to 600 mg or 800 mg compensates for the decrease in plasma levels caused by (daily) coadministration of rifampicin. In addition, a study of the pharmacokinetic interaction between moxifloxacin and rifapentine (another rifamycin) is warranted, considering that clinical trials involving this combination are underway. Finally, additional research should be performed to explore the activity and tolerability of higher doses of moxifloxacin, even in the absence of rifampicin coadministration.

Our study is limited by the design of the study, which did not allow discrimination between an effect on the moxifloxacin metabolism of rifampicin or isoniazid. In addition, the MIC and MPC values of M. tuberculosis for moxifloxacin were not determined but were based on previous findings. Therefore, pharmacodynamic ratios were partly derived. Furthermore, this study was not designed to assess the impact of moxifloxacin on the pharmacokinetics of rifampicin. Such an effect is not expected, because moxifloxacin does not induce any metabolism.

In conclusion, we showed a 31% decrease in exposure to moxifloxacin when combined with intermittently administered rifampicin and isoniazid in Indonesian patients with TB. This finding is in agreement with data from healthy volunteers [36], but the clinical relevance of this interaction has yet to be elucidated. A higher dose of moxifloxacin may possibly overcome the effect of rifampicin on the pharmacokinetics of moxifloxacin. Additional studies are warranted to assess the pharmacokinetics, dynamics, and tolerability of a higher dose of moxifloxacin when combined with rifampicin or other rifamycin derivatives.

**Acknowledgments**

We thank the patients, for their participation in this study; the staff at the outpatient clinic Balai Pengobatan Penyakit Paru-paru (BP4) and at Hasan Sadikin Hospital (Bandung, Indonesia), in particular Ni Sayu Dewi and Sri Yusnita Irdasari, for their cooperation and effort; and the technicians of the Department of Clinical Pharmacy of Radboud University Nijmegen Medical Centre (Nijmegen, The Netherlands), for the analysis of the plasma samples.

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**Table 2. Pharmacokinetic results for rifampicin and its main metabolite, desacetylrifampicin, in a cohort of 19 patients.**

<table>
<thead>
<tr>
<th>Drug or metabolite, pharmacokinetic parameter</th>
<th>Geometric mean value (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin AUC(_{0–24, h}), mg × h/L</td>
<td>35.7 (10.4–55.4)</td>
</tr>
<tr>
<td>C(_{\text{max}}), mg/L</td>
<td>6.9 (2.4–11.5)</td>
</tr>
<tr>
<td>C(_{\text{min}}), mg/L</td>
<td>0.34 (0.23–0.87)</td>
</tr>
<tr>
<td>t(_{\text{max}}), h</td>
<td>2.5 (1.5–6.0)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>12.7 (8.1–45.6)</td>
</tr>
<tr>
<td>V(_{\text{d/F}}), L</td>
<td>36.2 (23.9–91.8)</td>
</tr>
<tr>
<td>t(_{1/2}), h</td>
<td>2.0 (1.4–3.1)</td>
</tr>
</tbody>
</table>

| Desacetylrifampicin\(^b\) AUC\(_{0–24\, h}\), mg × h/L | 4.5 (0.0–7.1) |
| C\(_{\text{max}}\), mg/L | 0.92 (0.0–1.5) |
| C\(_{\text{min}}\), mg/L | 0.23 (0.0–0.39) |
| t\(_{\text{max}}\), h | 4.0 (0.0–6.0) |
| t\(_{1/2}\), h | 1.94 (0.0–3.1) |

| Ratio of desacetylrifampicin to rifampicin AUC\(_{0–24\, h}\), mg × h/L | 0.13 (0.0–0.26) |
| C\(_{\text{max}}\), mg/L | 0.12 (0.0–0.21) |

**NOTE.** Data are for study phase 1, in which patients received a combination of 400 mg of moxifloxacin administered once daily and 600 mg of isoniazid and 450 mg of rifampicin administered 3 times weekly. AUC\(_{0–24\, h}\), 24-h area under the concentration-time curve; C\(_{\text{max}}\), highest observed plasma concentration; C\(_{\text{min}}\), trough plasma concentration at 24 h after intake of study medication; CL/F, total clearance; F, bioavailability; t\(_{\text{max}}\), time at which C\(_{\text{max}}\) occurs; t\(_{1/2}\), elimination half-life; V\(_{\text{d/F}}\), volume of distribution.

\(^a\) Median and range.

\(^b\) Desacetylrifampicin was not found in 4 subjects.
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