Comparison of the *in vitro* activities of rifapentine and rifampicin against *Mycobacterium tuberculosis* complex

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The *in vitro* activity of rifapentine for 44 clinical isolates of *Mycobacterium tuberculosis* complex was compared with that of rifampicin using the Bactec radiometric method and the absolute concentration method for susceptibility testing. Twenty-nine *M. tuberculosis*, 11 *Mycobacterium bovis* and four *Mycobacterium africanum* strains were studied. Control tests showed that rifapentine was stable for 14 days in 7H9 broth and for 3 weeks in 7H10 agar medium. The 44 *M. tuberculosis* complex strains were more susceptible to rifapentine than to rifampicin, irrespective of the testing method. In the radiometric system, the MIC50 and MIC90 of rifapentine for *M. tuberculosis* complex strains were one or two two-fold dilutions lower than those of rifampicin (0.06–0.125 mg/L versus 0.25 mg/L, respectively). By the absolute concentration method, the MIC50 and MIC90 of rifapentine for *M. tuberculosis* complex strains were two two-fold dilutions lower than those of rifampicin (0.125–0.25 mg/L versus 0.5–1 mg/L, respectively). The MIC90 of rifapentine for the 44 *M. tuberculosis* complex strains was always ≤0.25 mg/L, irrespective of the method used, but the radiometric method was more reliable and more reproducible than the agar 7H10 method.

**Introduction**

Rifapentine is a new rifamycin derivative which has been approved recently by the Food and Drug Administration as an alternative to rifampicin in short-course therapy of tuberculosis. Rifapentine is active against all species of the *Mycobacterium tuberculosis* complex. Intermittent drug regimens against tuberculosis became possible with long-lasting rifamycins like rifapentine. There have been many reports on the antibacterial activity of rifapentine, and the advantages of rifapentine over rifampicin have been shown with *in vitro* and *in vivo* models. Broth-determined rifapentine MICs were two or three two-fold dilutions lower than those of rifampicin. The apparent elimination half-life of rifapentine is much longer than that of rifampicin in animals and humans, and plasma concentrations of rifapentine are above the MIC for 72 h after a single oral dose. Nevertheless, rifapentine penetrates macrophages less well than rifampicin; the activities of rifampicin and rifapentine are 20- and 26-fold lower, respectively, than *in vitro*. The purpose of this study was to determine the *in vitro* activity of rifapentine against clinical isolates of *M. tuberculosis* complex, including *M. tuberculosis*, *Mycobacterium bovis* and *Mycobacterium africanum*, in comparison with the activity of rifampicin. The Bactec radiometric method and the absolute concentration method were used to test mycobacterial susceptibility.

**Materials and methods**

**Mycobacterial strains**

Forty-four strains from the *M. tuberculosis* complex were included in this study, comprising 29 *M. tuberculosis* strains (27 fully susceptible clinical isolates, one isoniazid-resistant strain, and one isoniazid- and streptomycin-resistant strain), four clinical isolates of *M. africanum* and 11 *M. bovis* strains. Two quality control (QC) strains were also tested: *M. tuberculosis* H37Rv ATCC 27294 and *M. bovis* ATCC 35734, which were both fully susceptible.

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Antibiotics

Rifapentine and rifampicin were obtained from Hoechst Marion Roussel (Romainville, France). Stock solutions were prepared in methanol and were diluted in distilled water before addition to culture media.

Media

Two commercially available media were used: (i) 7H12 broth in 12B vials (Becton Dickinson, Sparks, MD, USA) and (ii) Middlebrook–Cohn 7H10 agar medium (Becton Dickinson) with 10% oleic acid–albumin–dextrose–citrate (OADC; Difco Laboratories, Detroit, MI, USA). The agar medium (2.5 mL/well) was distributed in 12-well tissue culture plates (Polylabo; Paul Block & Cie, Strasbourg, France) so that six wells contained six different drug concentrations for both rifapentine and rifampicin. Drug-free controls were set up in two separate plates.

Susceptibility testing by the absolute concentration method

This procedure was performed by inoculating 7H10 agar medium containing rifampicin and rifapentine (concentrations from 0.03 to 1 mg/L) or without drug with M. tuberculosis complex (at an inoculum of $10^3$–$10^4$ cfu/well). The plates were incubated in 5–10% CO$_2$ for 3 weeks at 37°C. Susceptibility to these compounds was defined as growth of $<20$ cfu at a particular concentration of compound.$^{13}$

Guthertz et al. demonstrated that 30% of batches of OADC led to interpretations of both false-susceptible and false-resistant isolates.$^{14}$ Butler et al. established a correlation between the ability of OADC to support the growth of Bacillus subtilis and its ability to support mycobacterial growth.$^{15}$ Each batch of OADC was tested for its ability to support the growth of B. subtilis ATCC 6633, as described previously.$^{16}$

A representative sample of each batch of plates was incubated for 48 h at 37°C and checked for sterility.$^{16}$

Susceptibility testing by the radiometric Bactec technique

Standardized Bactec technology was used for determining >99% growth inhibition. Both compounds were added to Bactec vials by transferring 0.1 mL of the rifampicin solutions (final concentrations from 0.03 to 1 mg/L) or rifapentine solutions (0.015–0.5 mg/L). Preliminary experiments showed that rifapentine had high activity against one M. tuberculosis strain with radiometric MICs as low as 0.03 mg/L, which allowed us to use a lower MIC range for rifapentine (unpublished data). The source of the inoculum was a positive Bactec vial inoculated with the strains. Culture vials containing antibiotics as well as one drug-free control vial were inoculated to give a final concentration of approximately $3 \times 10^5$ to $10^6$ cfu/mL. A second control vial was inoculated with a 1/100 dilution of the bacteria. The $^{14}$CO$_2$ produced by mycobacteria was recorded daily for 8–10 days and expressed as the growth index (GI), which ranged from 1 to 999. The MIC was defined as the lowest drug concentration in the presence of which the overnight increase in GI was lower than in the 1/100 dilution of the drug-free control, when the latter had reached a GI of $>30$.$^{16}$ Vials were tested daily for up to 12 days, which is the maximum incubation time for antimycobacterial susceptibility testing.

Reproducibility of MICs with rifapentine and rifampicin stock solutions

Reproducibility was measured against one M. tuberculosis strain with drug stock solution. Rifapentine and rifampicin stock solutions were prepared every 3 weeks and frozen at –80°C. Every week, a tube of the frozen stock solution was thawed and diluted with water to achieve the desired concentrations. Both compounds were added to Bactec vials (rifapentine final concentrations from 0.015 to 0.5 mg/L, rifampicin final concentrations from 0.03 to 0.5 mg/L). The MICs of rifapentine and rifampicin were determined for the M. tuberculosis clinical isolate HBD 40 using the radiometric method described above.

Measurement of stability of rifapentine and rifampicin

Stability in 12B vials. Appropriate dilutions of rifampicin and rifapentine were added to a series of 12B vials to achieve final concentrations of 0.5 or 1 mg/L. The vials were incubated for 12 days at 37°C. The concentration of each compound was determined every other day with a microbiological assay, using the agar diffusion method with B. subtilis ATCC 6633 as the test strain.$^{17}$

Stability in tissue culture plates. Freshly prepared rifapentine- and rifampicin-containing plates were kept at 4°C and at 37°C. The potency of the antimicrobials was monitored using the absolute concentration method. The B. subtilis ATCC 6633 test strain was chosen for its rapid growth in 7H10 medium and its high susceptibility to rifampicin. 7H10 agar medium without drugs or containing rifampicin and rifapentine (final concentrations from 0.015 to 0.5 mg/L) was inoculated with a B. subtilis ATCC 6633 suspension ($10^3$–$10^4$ cfu/well). Plates were incubated in 5–10% CO$_2$ for 24–48 h at 37°C. Susceptibility to these compounds was defined as growth of $<20$ cfu at a particular concentration of compound.$^{13}$ Susceptibility tests were repeated every other day for 4 weeks. The MICs of rifapentine and rifampicin against B. subtilis ATCC 6633 were compared.

Statistical analysis

Multiple range tests were performed with Statgraphics software for the M. tuberculosis and M. bovis strains.

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## Results

*Stability of drugs in Bactec vials and in plates kept at 37°C and 4°C*

In the Bactec system, MICs of rifampicin and rifapentine for the *M. tuberculosis* clinical isolate HBD 40 were 0.06 and 0.25 mg/L, respectively, and remained stable throughout the 3 week test period. In 12B vials, the concentration of rifampicin and rifapentine had decreased slightly (<50%) by day 12, corresponding to an MIC increase of one dilution (Table I). MICs of rifapentine and rifampicin against *B. subtilis* ATCC 6633 determined with the plates stored at 37°C were one two-fold dilution higher on days 11–19 of storage than on days 1–9 (0.25 and 0.125 mg/L, respectively), and two two-fold dilutions higher on days 21–25 than on days 1–9 (0.5 mg/L versus 0.125 mg/L) (Table II). Using plates kept at 4°C for 19 days, MICs of both compounds were one two-fold dilution higher than using newer plates (0.125 mg/L and 0.06 mg/L, respectively). These results showed that, when incorporated in 7H10 medium, the two compounds remained relatively stable for 3 weeks.

### MICs of rifapentine and rifampicin for QC strains

For *M. tuberculosis* H37Rv (ATCC 27294), MICs of rifapentine were 0.06 mg/L by both the 7H10 absolute concentration and radiometric methods. MICs of rifapentine were 0.125 mg/L in the Bactec system and 0.5 mg/L in the 7H10 absolute concentration method. MICs of rifapentine and rifampicin for *M. bovis* ATCC 35734 did not exceed 0.03 mg/L by either method and were 0.06 and 0.25 mg/L, respectively, on 7H10 agar plates.

### MICs of rifapentine and rifampicin for 29 fully susceptible *M. tuberculosis* strains

The results for the 29 *M. tuberculosis* isolates are listed in Table III. MICs of rifapentine were lower than those of rifampicin. Observed on 7H10 agar plates were higher than those observed in the Bactec radiometric system. The MIC<sub>50</sub> and MIC<sub>90</sub> of rifapentine were 0.06 mg/L in the radiometric system; MICs were only one or two two-fold dilutions higher with the absolute concentration method on 7H10 agar (0.125 and 0.25 mg/L, respectively). The MIC<sub>50</sub> and MIC<sub>90</sub> for rifampicin were 0.25 mg/L with the radiometric method and 0.5–1 mg/L on 7H10 agar plates. For the two resistant strains (one resistant to isoniazid and one to both isoniazid and streptomycin), MICs of rifapentine and rifampicin were in the same range as for the fully susceptible clinical isolates irrespective of the method.

### MICs of rifapentine and rifampicin for 11 fully susceptible *M. bovis* clinical isolates

MICs for *M. bovis* isolates are listed in Table III. Eleven *M. bovis* strains were studied: 10 clinical isolates and one *M. bovis* BCG strain. The MIC<sub>50</sub> and MIC<sub>90</sub> were comparable to those obtained for *M. tuberculosis* strains with both drugs by either susceptibility testing method, except for the MIC<sub>90</sub> of rifapentine, which was one two-fold dilution higher (0.125 mg/L versus 0.06 mg/L) in the radiometric system. Like the QC *M. bovis* ATCC 35734 strain, the *M. bovis* BCG strain was more susceptible to rifapentine than clinical isolates of *M. bovis* (MICs of 0.06 mg/L irrespective of the method).

### MICs of rifapentine and rifampicin for four fully susceptible *M. africanum* clinical isolates

MICs for *M. africanum* clinical isolates are shown in Table III. The MIC<sub>90</sub> of rifapentine and rifampicin were

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**Table I.** Stability of rifapentine and rifampicin in 12B vials, determined by bioassay

<table>
<thead>
<tr>
<th>Day</th>
<th>Rifapentine (mg/L)</th>
<th>Rifampicin (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
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</tr>
<tr>
<td>5</td>
<td>0.57</td>
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</tr>
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<td>8</td>
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</tr>
<tr>
<td>12</td>
<td>0.52</td>
<td>0.92</td>
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</tbody>
</table>

**Table II.** Stability of rifampicin and rifapentine in 7H10 agar plates stored at 37°C determined by their MICs for *B. subtilis* ATCC 6633

<table>
<thead>
<tr>
<th>Day</th>
<th>rifampicin (mg/L)</th>
<th>rifapentine (mg/L)</th>
</tr>
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<tbody>
<tr>
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<td>0.12</td>
</tr>
<tr>
<td>3</td>
<td>0.12</td>
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</tr>
<tr>
<td>5</td>
<td>0.12</td>
<td>0.12</td>
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<tr>
<td>7</td>
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<td>0.12</td>
<td>0.12</td>
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<tr>
<td>13</td>
<td>0.25</td>
<td>0.25</td>
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<tr>
<td>15</td>
<td>0.25</td>
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<tr>
<td>17</td>
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<td>0.25</td>
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<tr>
<td>19</td>
<td>0.25</td>
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<tr>
<td>21</td>
<td>0.5</td>
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<tr>
<td>23</td>
<td>0.5</td>
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<tr>
<td>25</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>27</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>29</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
</tr>
</tbody>
</table>
comparable to those for *M. tuberculosis* isolates, irrespective of the method used.

**Statistical analysis of the data**

Multiple range tests showed statistically significant differences at the 95.0% confidence level for rifapentine versus rifampicin, and for Middlebrook 7H10 agar versus Bactec 12B medium. MICs of rifapentine were significantly lower than MICs of rifampicin, irrespective of the method, and MICs of rifapentine and rifampicin were significantly higher in 7H10 medium than in the Bactec system.

**Discussion**

The Bactec radiometric method is a reliable and rapid method of testing the susceptibility of the *M. tuberculosis* complex. Drug susceptibility was determined using an adaptation of the conventional proportion method. The accuracy and reproducibility of the radiometric method are well known, at least for the four main antituberculosis drugs, namely streptomycin, isoniazid, rifampicin and ethambutol. In a recent report, Heifets et al. validated the determination of rifapentine MICs with the radiometric system, against QC strains and clinical isolates of *M. tuberculosis*. The purpose of our study was to determine the MICs of rifapentine and rifampicin for various clinical isolates using Bactec 12B medium. MICs of rifapentine were higher than MICs of rifampicin, irrespective of the method used.

Controls were included to validate the radiometric procedure. The stability of rifapentine in 12B vials was determined by a microbiological assay; the study period was 12 days, the maximum reporting time of the radiometric susceptibility test. The rifapentine concentration had decreased, but not by more than 50%, at the completion of the experiment. The good stability of rifapentine in 7H12 broth allowed us to interpret the MICs determined for the *M. tuberculosis* complex strains. The MICs of rifapentine were comparable (0.06 mg/L) for the *M. tuberculosis* and *M. bovis* clinical isolates tested, as for the two QC strains (ATCC 27294 and ATCC 35734). The MICs of rifapentine were identical (0.06 mg/L) for *M. tuberculosis* and *M. bovis*, but one two-fold dilution higher (0.125 mg/L) for *M. bovis*. The MICs of rifapentine and rifampicin were comparable (0.25 mg/L) for all the *M. tuberculosis* complex strains. The 46 *M. tuberculosis* complex strains tested were significantly more susceptible to rifapentine than to rifampicin in the radiometric system.

As judged by the absolute concentration method using Middlebrook and Cohn 7H10 agar medium, both rifapentine and rifampicin were relatively stable for 3 weeks (the MICs of rifapentine and rifampicin were two two-fold dilutions higher on day 25 than earlier in the study), but after 4 weeks their potency had decreased significantly (by three or more two-fold dilutions). The MICs of both compounds were one or two two-fold dilutions higher in 7H10 medium than in the Bactec system for most of the *M. tuberculosis* complex strains. These differences can be explained by loss of potency of agents with the delay in reading results.

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### Table III. MIC range, MIC<sub>50</sub> and MIC<sub>90</sub> of rifapentine and rifampicin for clinical mycobacterial strains

<table>
<thead>
<tr>
<th>Organism</th>
<th>n</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
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<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
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<tbody>
<tr>
<td><em>M. tuberculosis</em></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bactec</td>
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<td>0.06</td>
<td>0.03–0.125</td>
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<td>7H10 agar</td>
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<td>0.06–0.5</td>
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<td>0.125–1</td>
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<td><em>M. bovis</em></td>
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<td>0.125</td>
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<td>7H10 agar</td>
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<td><em>M. africanum</em></td>
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incubation time of 4–5 weeks was required for some strains with MICs four two-fold dilutions higher than Bactec MICs. Despite this lack of activity, the MIC<sub>50</sub> of rifapentine for the 46 <i>M. tuberculosis</i> complex strains was <0.25 mg/L, irrespective of the method used. For only one strain of <i>M. tuberculosis</i> was the MIC 0.5 mg/L. Heifets <i>et al.</i> suggested that a breakpoint of 0.5 mg/L for rifapentine makes a clear distinction between susceptible and resistant <i>M. tuberculosis</i> strains irrespective of the testing method. Our findings are in agreement with these results. However, the radiometric method was more reliable and more reproducible than the agar 7H10 method. The QC tests showed that the compounds were more stable in 12B vials than in agar plates. Moreover, for some isolates, because of their lower rate of growth, an incubation time of 4–5 weeks is required for the latter method, so a decrease in potency could be a problem.

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References


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