In Vitro Activities of Several New Macrolide Antibiotics against *Mycobacterium avium* Complex

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The in vitro activities of 12 macrolide compounds against 28 *Mycobacterium avium* complex (MAC) strains isolated from patients with acquired immunodeficiency syndrome were determined by the conventional proportion method and by the BACTEC method. Clarithromycin (A-56268; TE-031), a new macrolide compound, was the most active agent tested, inhibiting 90% of strains at an MIC of 4 μg/ml by the BACTEC method. Roxithromycin (RU 28965) and erythromycinylamine were active at an MIC of 16 μg/ml for 90% of strains. The organism showed high levels of resistance to most other macrolide compounds.

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TABLE 1. Comparative in vitro activities of 12 antimicrobial agents against 28 MAC strains by BACTEC and agar dilution methods

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (µg/ml)*</th>
<th>Range</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-Dihydro-20-O-phenyl macr oxylin</td>
<td>32–64</td>
<td>≥64</td>
<td>≥64</td>
<td>≥64</td>
</tr>
<tr>
<td>20-Dihydro-20-O-phenyl desmycosin</td>
<td>32–64</td>
<td>≥64</td>
<td>≥64</td>
<td>≥64</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>4–16</td>
<td>8 (16)*</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>23-Deoxy-5-O-mycaminosyl-tylonolide</td>
<td>32–64</td>
<td>≥64</td>
<td>≥64</td>
<td>≥64</td>
</tr>
<tr>
<td>9-N-(2-Methoxyethyl)erythromycylamine</td>
<td>32–64</td>
<td>≥64</td>
<td>≥64</td>
<td>≥64</td>
</tr>
<tr>
<td>20-Deoxy-20-dipropylaminodesmycosin</td>
<td>32–64</td>
<td>≥64</td>
<td>≥64</td>
<td>≥64</td>
</tr>
<tr>
<td>23-O-Acetyl-5-O-mycaminosyltylonolide</td>
<td>32–64</td>
<td>≥64</td>
<td>≥64</td>
<td>≥64</td>
</tr>
<tr>
<td>23-Demycinosylylosin</td>
<td>8–32</td>
<td>16</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>4–16</td>
<td>8 (16)*</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>8–32</td>
<td>16</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.25–4</td>
<td>2</td>
<td>4 (8)</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>32–64</td>
<td>32</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

*a 50% and 90%. MIC for 50% and 90% of isolates, respectively.

Although there were a few discrepancies between the two methods in MICs of some macrolide compounds, at higher drug concentrations (≥16 µg/ml) the discrepancies were inapparent. Table 2 shows an analysis of two methods of drug susceptibility testing. A ratio of the MIC of the proportion method to that of the radiometric method equal to unity indicates that both methods produced the same results. More than 50% of the strains tested (MIC, ≤32 µg/ml) had a ratio equal to unity. A ratio of 2 indicates that the proportion method MIC was double that of the radiometric method. The percentages of strains in this category (3 to 42%) varied with the type of drug. Few strains with a ratio of more than 2 were found. Considering the dilution error of one log₂, the discrepancies between the two methods are not major. In our hands, the radiometric method was suitable and reproducible. Some researchers have evaluated both methods with the following points of consideration (8, 10): binding of the drug in solid medium, deterioration of the drug owing to the prolonged incubation period, and rather crude evaluation of the result in the proportion method, suggesting that the radiometric method is superior. The radiometric system is rapid and reliable. The cell-to-drug interaction is three dimensional, and the results obtained are in semiquantifiable units. However, the system is relatively expensive and laborious. The problem of radioactive-waste disposal is also involved.

Our data regarding the in vitro activities of many of the newer macrolides are in general close to those reported by other investigators (2, 5). Although clarithromycin, a new macrolide, demonstrated excellent in vitro activity against all MAC isolates tested, clinical experience with this agent is lacking. Preliminary studies indicate that clarithromycin is well absorbed when administered orally and consistently attains levels of 2 µg/ml in blood at a dose of 400 mg and 4.4 µg/ml at a dose of 1,200 mg in human subjects. The serum half-life is 4.7 h, and the drug concentrates in lung tissue at approximately 10 times the concentration in serum (L. T. Sennello, S.-Y. Chu, D. S. Wilson, K. S. Laws, S. T. Bunnell, L. L. Varga, and K. Snyder, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 419, 1986). In another preliminary study involving human subjects, clarithromycin proved to be a relatively safe drug with mild side effects, such as headache, nausea, and rash in a few volunteers (S.-Y. Chu, L. T. Sennello, S. T. Bunnell, L. L. Varga, D. S. Wilson, R. L. Deaton, K. E. Rice, S. D. Gupta, M. J. Klepper, D. M. Moyse, and K. Tolman, 28th ICAAC, abstr. no. 136, 1988). Because drug combination therapy is almost the rule in the treatment of MAC infections and drugs with different mechanisms of actions are desirable, clarithromycin is a potential therapeutic partner.

LITERATURE CITED


