Antimicrobial Activity of Ro 15-8074, Active Metabolite of a New Oral Cephalosporin (Ro 15-8075), against 7,775 Recent Clinical Isolates

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Susceptibility testing of 7,775 recent clinical isolates from four medical centers showed Ro 15-8074 to be 2- to >8-fold more active than either cefaclor or cefuroxime against the Enterobacteriaceae. Ro 15-8074 MICs for 50% of the strains tested were ≥32 μg/ml for Staphylococcus spp., enterococci, Pseudomonas aeruginosa, and Pseudomonas maltophilia. β-Lactamase hydrolysis experiments failed to demonstrate significant Ro 15-8074 inactivation by commonly encountered chromosomal or plasmid-mediated enzymes (P99, K1, K14, TEM, and CARB).

Ro 15-8074 was furnished by Roy Cleeland of Hoffmann-La Roche Inc., Nutley, N.J. Other oral, parenteral, and reagent cephalosporins were acquired from their representative manufacturers. All drugs were tested in cation-supplemented Mueller-Hinton broth (8) in the active standard form found in vivo, i.e., sodium salts or free acids of cefaclor and cefuroxime.

β-Lactamase hydrolysis rates of various β-lactams were determined with a scanning spectrophotometer over the range of 254 to 482 nm at 37°C (6). Hydrolysis rates for Ro 15-8074 and cefotaxime were compared with those of nitrocefin and cephaloridine. Each cephalosporin substrate was tested at a concentration of 10⁻⁴ M in a 0.5 M phosphate buffer (pH 7.0). The β-lactamase preparations were made by methods described previously from organisms known to produce various Richmond and Sykes β-lactamase types (6, 12).

Susceptibility testing of the three oral cephalosporins (data not shown) against 2,428 staphylococci, streptococci, and enterococci demonstrated that Ro 15-8074 had little activity against S. aureus, coagulase-negative Staphylococcus spp., and the Enterococcus spp. (MIC for 90% of strains tested [MIC₉₀], >32 μg/ml). In contrast, cefuroxime and
table 1. Comparison of β-lactamase hydrolysis rates for two cephalosporins with those of control nitrocefin and cephaloridine

<table>
<thead>
<tr>
<th>Organism (β-lactamase)</th>
<th>Hydrolysis rate relative to cephaloridine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacter cloacae (P99)</td>
<td>Ro 15-8074 Cefotaxime Nitrocefin</td>
</tr>
<tr>
<td>Escherichia coli (TEM-1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Escherichia coli (TEM-2)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Klebsiella oxytoca (K-1)</td>
<td>0.7</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (CARB-1)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (CARB-2)</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

* β-Lactamase hydrolysis was determined by the UV spectrophotometric method using 258 to 482 nm at 37°C. Reaction mixtures were at a volume of 1.0 ml with 10⁻⁴ M cephalosporin substrate in 0.05 M (pH 7) phosphate buffer.

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cefaclor had antistaphylococcal spectra covering 86 to 93% and 75 to 83% of the strains, respectively. All three cephalosporins tested were totally ineffective against the enterococci. Ro 15-8074 did show moderate activity (MIC₉₀, 4.0 µg/ml) against 74 strains of Streptococcus agalactiae, Streptococcus bovis, and Streptococcus pyogenes. The three cephalosporins were 2- to >16-fold more active against these three species.

The results of testing enteric organisms are presented in Fig. 1. Ro 15-8074 was generally 2- to >8-fold more active than either cefuroxime or cefaclor against the 16 tabulated species or groups of Enterobacteriaceae. If an MIC of ≤8 µg/ml was used to indicate susceptibility to all three cephalosporins, Ro 15-8074 would inhibit (MIC for 50% of strains tested [MIC₅₀]) 15 of 16 organism groups. Only the Enterobacter spp., Citrobacter freundii, Morganella morganii, and Serratia marcescens strains had ≥7% resistance to Ro 15-8074. None of cephalosporins were active against P. aeruginosa and Pseudomonas maltophilia (data not shown). Ro 15-8074 had an MIC of ≤8 µg/ml against approximately three-fourths of the Acinetobacter strains. Ro 15-8074 was also active against nine strains of Aeromonas hydrophila (MIC₅₀, 0.5 µg/ml) and against Pseudomonas cepacia (MIC₅₀, 4.0 µg/ml).

The seven β-lactamase preparations used in the hydrolysis study minimally inactivated Ro 15-8074 and ceftaxime, the aminothiazolyl-methoxyimino cephalosporins. The continued search for orally absorbed cephalosporins with expanded antimicrobial spectra has produced several new agents, including the cefuroxime axetil ester, LY164846, and cefixime (FK 027) (1, 3–5). Each has a selected spectrum or potency advantage over earlier oral cephalosporins such as cephalaxin or cefaclor, but their serum concentrations generally remain lower (3, 4). We also found Ro 15-8074 to have a somewhat unique antimicrobial spectrum directed principally against the enteric bacilli (13). The drug inhibited 90.7% of all Enterobacteriaceae tested at ≤8 µg/ml compared with only 78.4 and 70.1% for cefuroxime and cefaclor, respectively. This activity advantage may be less pronounced if the absorption of the Ro 15-8074 ester does not produce concentrations in serum compatible with an MIC breakpoint of ≤8 µg/ml. This latter breakpoint is used for cephalaxin, cephradine, cefadroxil, and cefaclor, but it was necessary to reduce the breakpoint to ≤1.0 µg/ml for cefixime because of inferior oral pharmacokinetics (3).

Studies reported elsewhere showed Ro 15-8074 to be very active against H. influenzae and Neisseria gonorrhoeae, including β-lactamase-producing strains (7, 9, 10, 13). The β-lactamase hydrolysis studies reported here confirm a general enzyme stability of Ro 15-8074 most similar to cefotaxime. Clinical trials with this agent should be considered for infections caused by the Enterobacteriaceae (most urinary tract infections), N. gonorrhoeae (genital infections), and fastidious gram-negative organisms, such as Haemophilus spp. or Branhamella catarrhalis (selected respiratory infections).

**LITERATURE CITED**


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**FIG. 1.** MIC₉₀ results for Ro 15-8074 (●), cefuroxime (△), and cefaclor (□) tested against 4,217 recent Enterobacteriaceae isolates. Vertical lines represent possible MIC breakpoints. The other Enterobacter species were 19 strains each of E. agglomerans and E. sakazakii. A total of 29 strains of enteric bacilli from five other species (fewer than 10 strains per species) were not tabulated here.