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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Received 21 July 1986/Accepted 23 September 1986

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 \( \geq 3.2 \mu g/ml \) for Staphylococcus spp., enterococci, Pseudomonas aeruginosa, and Pseudomonas maltophilia. \( \beta \)-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.

\( \beta \)-Lactamase hydrolysis rates of various \( \beta \)-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 \( \beta \)-lactamase preparations were made by methods described previously from organisms known to produce various Richmond and Sykes \( \beta \)-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 2, 4 to 32 \( \mu g/ml \)).

TABLE 1. Comparison of \( \beta \)-lactamase hydrolysis rates for two cephalosporins with those of control nitrocefin and cephaloridine

<table>
<thead>
<tr>
<th>Organism (( \beta )-lactamase)</th>
<th>Hydrolysis rate relative to cephaloridine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entero bacter cloacae (P99)</td>
<td>0.3</td>
</tr>
<tr>
<td>Escherichia coli (TEM-1)</td>
<td>0.9</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>Klebsiella oxytoca (K-14)</td>
<td>&lt;0.1</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>

* \( \beta \)-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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cefalexin 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 (MIC<sub>50</sub>, 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 [MIC<sub>50</sub>]) 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 (MIC<sub>50</sub>, 0.5 μg/ml) and against Pseudomonas cepacia (MIC<sub>50</sub>, 4.0 μg/ml).

The seven β-lactamase preparations used in the hydrolysis study minimally inactivated Ro 15-8074 and cefotaxime, the aminothiazol- méthoxymimo 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 cephalins such as cephalexin 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 cephalexin, cephadrine, 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


