Comparative In Vitro Activity of Five Cephalosporins Against Lactobacilli

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Of five parenteral cephalosporins tested against 43 lactobacilli, cephaloridine, cefazolin, and cefamandole were the most active inhibitory and bactericidal agents. Timed-kill analysis revealed a slow bactericidal effect, with significant declines in mean minimal bactericidal concentration values at 48 h versus 24 h.

Lactobacilli are being increasingly recognized as important pathogens in human infections (1, 2, 10, 12). An interesting phenomenon noted in many previously reported cases of lactobacillemia was the therapeutic difficulty in eradicating this organism from deep-seated foci, especially endocardium, despite seemingly appropriate single-drug regimens and serum antibiotic concentrations exceeding the minimal inhibitory concentrations (MICs). Combination therapy with penicillins and aminoglycosides appears efficacious against the lactobacilli (2); however, optimum therapy in penicillin-allergic patients has not been delineated. To investigate this problem, the comparative inhibitory and bactericidal activity of five cephalosporin agents was studied against 43 clinical lactobacillus isolates by a modified broth dilution technique.

All 43 strains of lactobacilli were clinical isolates from a variety of body sites, including blood, genital tract, oropharynx, ascitic fluid, lymph node, and brain tissue. Thirteen were obtained from the clinical laboratory of Harbor General Hospital, Torrance, Calif., whereas the remaining 30 organisms were kindly provided by the following investigators: Elizabeth P. Cato, Blacksburg, Va.; Robert E. Weaver, Atlanta, Ga.; Jack P. London, Bethesda, Md.; and M. Elisabeth Sharpe, Reading, England.

The lactobacilli were identified by typical appearance on Gram stain and by biochemical reactions according to Bergey's criteria (8). Identification of species was according to classification of Holdeman and Moore (5). The following strains of lactobacilli were used in this study: Lactobacillus casei (26 strains), L. plantarum (6 strains), L. acidophilus and L. minutis (3 strains each), L. ferments and L. brevis (2 strains each) and L. leichmanii (1 strain). All of the L. casei and L. plantarum and two of the three L. minutis isolates were facultative anaerobes; the remainder were strict anaerobes.

Maintenance and transfer of the lactobacilli before susceptibility testing, media, and reagents, as well as broth dilution and statistical techniques for determining and comparing the MICs and minimal bactericidal concentrations (MBCs), were essentially the same as previously reported (3). In addition, both 24- and 48-h MBCs were determined for each isolate to assess timed killing of the lactobacilli. As in our prior study, a final inoculum of ~ 2 × 10⁵ colony-forming units per antibiotic-containing tube was used (3).

Serial twofold dilutions were made of all antibiotics and added to the broth under strictly anaerobic conditions. After addition of the lactobacillus inocula, the final range of drug concentrations was 0.312 to 320 µg/ml for each agent. Cefamandole, cefazolin, and cefalothin were kindly provided by Eli Lilly & Co. (Indianapolis, Ind.), cefoxitin was obtained from Merck, Sharp, and Dohme Research Laboratories (West Point, Pa.), and cephalothin was purchased from USP Standards (Rockville, Md.).

The cumulative percent of strains inhibited and killed by these five cephalosporin agents are summarized in Table 1. By employing the generally attainable serum levels of these antibiotics (20 µg/ml [6, 7, 11]) as susceptibility "breakpoints," the following data were obtained. For cephalothin, cefazolin, cefamandole, and cephaloridine, 97 to 100% of strains were inhibited by ≤20 µg/ml; for cefoxitin, only 14% of isolates were inhibited by ≤20 µg/ml.

On timed-kill analysis, there was no change in the 24- versus 48-h MBCs for cephalothin and cefoxitin. However, for cefazolin, cefamandole, and cephaloridine, the 48-h MBCs were significantly lower than those obtained at 24 h (range, P < 0.05 to P < 0.01).

When statistically compared to the four other cephalosporins tested, cephapridine was the most active inhibitory and bactericidal agent (P
< 0.005 and \( P < 0.0025 \), respectively). Cefazolin and cefamandole were of intermediate inhibitory and bactericidal efficacy, being significantly more active than either cefalothin (\( P < 0.005 \)) or cefoxitin (\( P < 0.0005 \)).

The "timed-kill" data in the present investigation and information from our prior studies (2, 3) have confirmed that many lactobacilli are "tolerant," i.e., they possess high MBC:MIC ratios and are slowly killed by cell wall-active antimicrobial agents (9). For cefaloridine, cefamandole, and cefazolin, there were statistically significant declines in the mean MBCs between 24 and 48 h, with MBCs for these three agents falling into the serum-achievable range. In contrast, the 24- and 48-h MBCs for cefoxitin and cefalothin were not different and remained 10 to 30 times higher than clinically attainable levels.

Clinically, lactobacillemias associated with deep-seated infectious foci, especially the endocardium, have been relatively refractory to high-dose, parenteral, single-drug regimens despite readily achievable MICs to these agents (1, 2, 10, 12). Penicillin-aminoglycoside combinations are recommended as the treatment of choice in such situations (2). Based on our in vitro data and if confirmed by further in vivo studies, cefaloridine would appear to be indicated in the therapy of serious lactobacillus infections in penicillin-allergic patients. Should preexisting or developing nephrotoxicity (6, 7) contraindicate the use of cefaloridine, high doses of cefazolin or cefamandole are reasonable alternative agents.

Cefazolin is particularly attractive in this regard, due to the high peak serum levels, prolonged serum half life, and superior tissue penetration in comparison to other cephalosporins (4, 7).

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**LITERATURE CITED**


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**Table 1. Comparative in vitro activity of five cephalosporins against 43 lactobacilli**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cumulative % of strains inhibited by:</th>
<th>Cumulative % of strains killed by:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \leq 0.03^a ) 1.25 5 20 80</td>
<td>( \leq 0.03^a ) 1.25 5 20 80</td>
</tr>
<tr>
<td>Cefalothin</td>
<td>2 9 95 100 100</td>
<td>2 2 2 15 28</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>13 32 65 100 100</td>
<td>0 27 29 54 81</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>11 20 76 97 100</td>
<td>2 13 27 59 89</td>
</tr>
<tr>
<td>Cefaloridine</td>
<td>32 74 97 97 100</td>
<td>8 32 75 86 97</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>2.5 2.5 7 14 32</td>
<td>2.5 2.5 2.5 2.5 7</td>
</tr>
</tbody>
</table>

\(^a\) 48-h MBC.

\(^b\) Concentration of cephalosporin in micrograms per milliliter.