Gemifloxacin Is Efficacious against Penicillin-Resistant and Quinolone-Resistant Pneumococci in Experimental Meningitis

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In experimental rabbit meningitis, gemifloxacin penetrated inflamed meninges well (22 to 33%) and produced excellent bactericidal activity (change in log₁₀ [Δlog₁₀ CFU/ml/h, −0.68 ± 0.30 [mean and standard deviation]), even superior to that of the standard regimen of ceftriaxone plus vancomycin (−0.49 ± 0.09 Δlog₁₀ CFU/ml/h), in the treatment of meningitis due to a penicillin-resistant pneumococcal strain (MIC, 4 mg/liter). Even against a penicillin- and quinolone-resistant strain, gemifloxacin showed good bactericidal activity (−0.48 ± 0.16 Δlog₁₀ CFU/ml/h). The excellent antibacterial activity of gemifloxacin was also confirmed by time-kill assays over 8 h in vitro.

Before the emergence of penicillin-resistant pneumococci, penicillin was usually the first-line antibiotic in the treatment of pneumococcal infections. The global increase of resistant pneumococci has jeopardized the treatment of pneumococcal infections (3). Additional resistance to cephalosporins has further limited therapeutic options for penicillin-resistant isolates. Despite the limitations of the actual therapeutic modalities, β-lactam antibiotics remain the first-line drugs for pneumococcal diseases, except when penetration into infected tissues is limited, as is the case in meningitis. At present, a combination of vancomycin and a cephalosporin is recommended for meningitis due to resistant strains (3, 10). An alternative regimen based on monotherapy would represent significant progress.

Especially due to its activity against many gram-positive microorganisms, including penicillin-resistant pneumococci, gemifloxacin, a new quinolone, is one of the most interesting candidates [N. Brenwald, M. J. Gill, F. Boswell, and R. Wise, J. Antimicrob. Chemother. 44(Suppl. A):145, 1999; D. Felmingham, M. J. Robbins, C. Dencer, H. Salman, I. Mathias, and G. L. Ridgway, J. Antimicrob. Chemother. 44(Suppl. A):131, 1999]. Little is known about the penetration of gemifloxacin into inflamed meninges. The aims of this study were to investigate the kinetics of gemifloxacin in the subarachnoid space and to test its bactericidal activity against pneumococci resistant to penicillin and to quinolones in the rabbit meningitis model. The standard regimen consisted of ceftriaxone combined with vancomycin.

Strains. The pneumococcal strain (WB4) was originally isolated from a patient with pneumonia at the University Hospital of Bern, Bern, Switzerland. The MICs (milligrams per liter) for this strain were as follows: penicillin, 4; ceftriaxone, 0.5; vancomycin, 0.12 to 0.25; trovafloxacin, 0.12; ciprofloxacin, 0.5; and gemifloxacin, 0.015. A quinolone-resistant strain was obtained by sequential exposure of parental strain WB4 to trovafloxacin. High-level resistance was conferred by point mutations in ParC (Ser79→Phe) and in GyrA (Ser81→Phe) (5).

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CSF was 0.7 mg/liter and decreased progressively to 0.12 mg/liter in the animals (5.9 versus 2.3 mg/liter) (8). The highest level in serum was higher in rabbits, although the peak level in serum was 2.5 mg/liter at 8 h. The serum AUC from 0 to 8 h (AUC 0–8) of 12.2 mg·h/liter was reached, comparable to the trough level of 0.45 mg/liter at 8 h. The CSF drug concentration/MIC ratios ranged between 46 and 8.

A higher dose of gemifloxacin (30 mg/kg) was chosen in order to maintain levels in CSF above the MIC (0.5 mg/liter for the quinolone-resistant strain) over the entire treatment period. The kinetics for 30 mg of gemifloxacin/kg are shown in Fig. 2. In serum, gemifloxacin peaked at 12.2 mg/liter and declined to 2.35 mg/liter after 8 h. The serum AUC 0–8 was 41 mg·h/liter. The peak level in CSF was 2.5 mg/liter and the trough level was 0.45 mg/liter at 8 h. The CSF drug concentration/MIC ratios ranged between 5 and 0.9. After one injection of 30 mg/kg, the penetration into the CSF was 33% ± 5%. The better CSF penetration at the higher dose (30 mg/kg) might be related to the drastic increase in the AUC 0–8 with a dose of 30 mg/kg (41 versus 12.2 mg·h/liter) in rabbits and might be due to an oversaturation of protein binding (protein binding of gemifloxacin in rabbits, 50 to 60%; Glaxo SmithKline Company, personal communication). Increasing the dose from 320 to 640 mg per os in humans led to only a doubling of the AUC (2). The doses of ceftriaxone and vancomycin used were standard doses that have been used in previous studies with the same model (4, 7, 9) and that correspond to high doses in humans (1, 13).

The killing rates for the different treatment groups are summarized in Table 1. Gemifloxacin produced highly bactericidal activity and managed to sterilize the CSF of 7 out of 11 rabbits after 8 h. All animals in the gemifloxacin group survived. It is interesting that gemifloxacin monotherapy was significantly superior to the standard regimen of ceftriaxone combined with vancomycin for the penicillin-resistant strain. On the other hand, the standard regimen was slightly but not significantly superior to gemifloxacin monotherapy for the penicillin- and quinolone-resistant mutant.

In vitro, gemifloxacin had excellent bactericidal activity against penicillin-resistant pneumococci at concentrations per hour and as the killing rate over 8 h. A value of 1.7 (log10 limit of detection) was assigned to the first sterile CSF sample, and a value of 0 was assigned to any following sterile sample. The results are expressed as means and standard deviations. Statistical significance was determined by the Newman-Keuls test.

Measurement of antibiotic levels in CSF. Antibiotic concentrations in CSF were determined by the agar diffusion method. Standard curves were determined for saline with 5% rabbit serum in order to mimic the CSF protein concentration (12). Bacillus subtilis (ATCC 6633) was used as a test strain for gemifloxacin (14). The intra- and interday variabilities of this method were less than 10%. The limit of detection for gemifloxacin was 0.05 mg/liter.

In vitro assays. The pneumococcal strains (penicillin-resistant strain WB4 and the quinolone-resistant strain) over the entire treatment period. As determined by comparison of serum and CSF AUCs, the penetration of gemifloxacin into inflamed meninges was 22%.
above the MIC (5 and 10 times the MIC) in time-kill assays over 8 h. Concentrations 5 and 10 times the MIC led to a dose-dependent decrease in the viable cell count over 8 h (3.8 and 5.25 log_{10} CFU/ml, respectively). Even against the quinolone-resistant strain, gemifloxacin showed good activity at concentrations above the MIC (3.9 and 4.75 log_{10} CFU/ml at 5 and 10 times the MIC, respectively).

The good penetration of gemifloxacin into the CSF (22 to 33%) and its efficacy in vitro and in our animal model qualify gemifloxacin as a potential therapeutic option for the treatment of meningitis, especially when resistant strains are involved.

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REFERENCES


TABLE 1. Single-drug and combination therapy against penicillin- and quinolone-resistant S. pneumoniae in experimental meningitis

<table>
<thead>
<tr>
<th>Strain</th>
<th>Antibiotic</th>
<th>No. of rabbits tested</th>
<th>Mean ± SD</th>
</tr>
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<tbody>
<tr>
<td>Penicillin resistant</td>
<td>None (control)</td>
<td>10</td>
<td>6.38 ± 0.63</td>
</tr>
<tr>
<td></td>
<td>Gemifloxacin</td>
<td>11</td>
<td>5.28 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone + vancomycin</td>
<td>6</td>
<td>5.96 ± 0.93</td>
</tr>
<tr>
<td>Penicillin and quinolone resistant</td>
<td>None (control)</td>
<td>5</td>
<td>5.67 ± 0.63</td>
</tr>
<tr>
<td></td>
<td>Gemifloxacin</td>
<td>9</td>
<td>6.15 ± 0.20</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone + vancomycin</td>
<td>5</td>
<td>6.09 ± 0.35</td>
</tr>
</tbody>
</table>

a P value for comparisons against all groups, <0.05.
b P value for comparisons of gemifloxacin against ceftriaxone-vancomycin groups, <0.03.
c P value was not significant.