Penetration of Cefuzoname into the Cerebrospinal Fluid of Rabbits

TSUNEKAZU HARUTA,1 HATSUMI YAMAMOTO,1 KAN-ETSU OKURA,1 SHIGEKAZU KUROKI,1 AND YUTAKA KOBAYASHI1,2*

Department of Pediatrics, Kobe Central Municipal Hospital,1 and Kobe City College of Nursing,2
Chuo-ku, Kobe 650, Japan

Received 2 January 1986/Accepted 30 April 1986

Concentrations of cefuzoname in cerebrospinal fluid (CSF) were determined in a total of 16 rabbits, 5 with healthy meninges, 5 with Staphylococcus aureus meningitis, and 6 with Escherichia coli meningitis. Mean percentages of the maximum concentration of the drug in CSF versus that in serum were 0.57, 3.37, and 4.40% for healthy rabbits, those with staphylococcal meningitis, and those with E. coli meningitis, respectively. The percentages of the area under the concentration-time curve of cefuzoname in CSF versus that in serum were, in the order of healthy group, staphylococcal meningitis group, and E. coli meningitis group, 0.61, 4.99, and 8.04% at 15 to 60 min, 1.44, 7.09, and 12.7% at 15 to 120 min, and 1.87, 8.07, and 15.8% at 15 to 180 min after administration, showing significant differences between the healthy and meningitis groups. All of the values in the E. coli meningitis group were greater than those of the staphylococcal meningitis group, but the differences were not significant. The ratios of the half-life of cefuzoname in CSF to that in serum were 2.10, 1.98, and 3.37 for the healthy, staphylococcal meningitis, and E. coli meningitis groups, respectively, with no significant difference among the three groups. Cefuzoname seems to be among the middle ranks of β-lactam agents as far as penetration rate is concerned; however, when its potent antibacterial activity and broad spectrum are taken into account, the concentrations in CSF in patients with meningitis seem worth examining.

Cefuzoname (L-105) is a new, injectable cephalosporin developed by Lederle (Japan) Ltd. The compound has a wide antibacterial spectrum covering most aerobic and anaerobic gram-positive and gram-negative bacteria. The activity of cefuzoname is similar to that of cefazolin against staphylococci and to those of broad-spectrum cephalosporins against gram-negative bacteria (M. Hikida, M. Inoue, and S. Mitsuhashi, Program Abstr. 24th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 733, 1984).

In view of the antibacterial potency of cefuzoname, it was thought that the compound might be effective in the therapy of purulent meningitis if it showed good penetration into cerebrospinal fluid (CSF); thus, the present study on its CSF penetration in rabbits was performed.

MATERIALS AND METHODS

Meningitis was experimentally induced by Staphylococcus aureus and Escherichia coli in healthy White rabbits weighing about 2 kg.

TABLE 1. Mean concentrations and standard deviations of cefuzoname in the serum and CSF of each group of rabbits

<table>
<thead>
<tr>
<th>Group (no. of rabbits)</th>
<th>Specimen</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (5)</td>
<td>Serum</td>
<td>186 ± 38.8</td>
<td>108 ± 28.4</td>
<td>58.8 ± 14.7</td>
<td>38.1 ± 13.0</td>
<td>27.7 ± 12.5</td>
<td>21.1 ± 10.7</td>
<td>8.98 ± 3.20</td>
<td>5.27 ± 2.51</td>
<td>3.33 ± 1.26</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.37 ± 0.10</td>
<td>0.50 ± 0.18</td>
<td>0.56 ± 0.20</td>
<td>0.92 ± 0.51</td>
<td>1.06 ± 0.85</td>
<td>0.94 ± 0.69</td>
<td>0.64 ± 0.51</td>
<td>0.54 ± 0.34</td>
<td>0.30 ± 0.26</td>
</tr>
<tr>
<td>Staphylococcal meningitis (5)</td>
<td>Serum</td>
<td>134 ± 52.0</td>
<td>62.8 ± 17.7</td>
<td>33.5 ± 10.8</td>
<td>15.8 ± 2.12</td>
<td>8.86 ± 2.18</td>
<td>6.56 ± 1.17</td>
<td>3.72 ± 0.76</td>
<td>2.23 ± 0.46</td>
<td>1.25 ± 0.46</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>1.19 ± 0.59</td>
<td>4.51 ± 3.95</td>
<td>2.43 ± 2.20</td>
<td>2.02 ± 1.90</td>
<td>1.73 ± 1.74</td>
<td>1.35 ± 1.21</td>
<td>0.98 ± 0.77</td>
<td>0.64 ± 0.56</td>
<td>0.48 ± 0.36</td>
</tr>
<tr>
<td>E. coli meningitis (6)</td>
<td>Serum</td>
<td>195 ± 74.3</td>
<td>112 ± 76.5</td>
<td>68.2 ± 57.7</td>
<td>36.5 ± 35.8</td>
<td>20.4 ± 19.8</td>
<td>14.5 ± 13.5</td>
<td>10.7 ± 12.4</td>
<td>6.11 ± 7.43</td>
<td>4.48 ± 5.29</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>7.93 ± 2.16</td>
<td>8.58 ± 3.85</td>
<td>7.81 ± 3.73</td>
<td>6.90 ± 3.64</td>
<td>6.34 ± 3.49</td>
<td>5.51 ± 2.85</td>
<td>4.78 ± 2.78</td>
<td>3.93 ± 2.60</td>
<td>3.05 ± 2.02</td>
</tr>
</tbody>
</table>

* Corresponding author.

0.5-ml sample of this cell suspension was inoculated into 10 rabbits intracisternally under anesthesia with thiamylal (15 mg/kg). E. coli meningitis was induced by using E. coli Miyamoto strains derived from a patient with meningitis. A 0.5-ml sample of a cell suspension containing 2 × 10⁵ CFU of E. coli per ml was inoculated into 10 rabbits intracisternally under anesthesia with thiamylal. Establishment of meningitis in the rabbits was confirmed macroscopically by autopsy after all samples of blood and CSF had been collected. Ten nontreated, healthy rabbits were used as controls.
A separate study on the CSF in three groups of three rabbits each revealed averages (in the order of healthy group, staphylococcal meningitis group, and *E. coli* meningitis group) of total cell count of 4,821, and 6,751/mm³, of protein of 27.3, 133, and 316 mg/dl, of glucose of 93.3, 62.7, and 63.7 mg/dl, and of CSF glucose/serum glucose of 54.2, 51.4, and 42.8%. Rabbits with staphylococcal meningitis were only mildly irritable with no evident signs of disease, all rabbits healed spontaneously, and *S. aureus* was not found in the CSF. However, meningitis was observed histologically. Rabbits with *E. coli* meningitis were deadly exhausted at 24 h after inoculation. If untreated, the animals would have died in about 48 h by an increase of *E. coli* in the CSF.

Over a period of about 5 min, cefuzoname (100 mg/kg) was infused through the ear vein into 10 rabbits with staphylococcal meningitis, 10 rabbits with *E. coli* meningitis, and 10 healthy rabbits. In infected rabbits the infusion was performed 24 h after inoculation. Samples of blood and CSF were collected at 15, 30, 45, 60, 75, 90, 120, 150, and 180 min after the start of antibiotic infusion. Blood was collected directly into four hematocrit tubes (75 mm long; Drummond Scientific Co., Broomall, Pa.), and CSF was collected by intracisternal puncture with a scalp vein needle (21 gauge; Terumo Co., Tokyo, Japan) while the rabbits were anesthetized with amobarbital (33 mg/kg). The volumes of the samples were about 200 µl each for blood and 50 µl each for CSF. Blood samples were centrifuged (Kubota Hematocrit KH/120A; Kubota Seisakusho, Tokyo, Japan) for 5 min at 10,000 rpm to obtain supernatants. CSF samples were placed directly on a microtiter plate (V form; Greiner Co., Nurtingen, Federal Republic of Germany). Those rabbits whose CSF samples were bloody when collected were excluded; thus, five rabbits of the healthy group, five of the staphylococcal meningitis group, and 6 of the *E. coli* meningitis group were analyzed.

The paper disk method was used to determine antibiotic concentrations. *E. coli* NIHJ strains, heart infusion agar (pH 7.4; Eiken Chemical Co., Ltd., Tokyo, Japan), and paper disks (6 mm in diameter; Toyo Seisakusho Co., Ltd., Tokyo, Japan) were used. For the standards, 1/15 M phosphate buffer solution (pH 7.0) was used. The lower limit of measurement was 0.0125 µg/ml.

**RESULTS**

Table 1 shows mean concentrations of cefuzoname in the serum and CSF of each group after intravenous administration of 100 mg/kg to individual rabbits, along with the standard deviations.

In all of the rabbits the maximum concentration (*C*ₘₐₓ) of the compound in serum was found at 15 min after administration, and the mean value was 186 ± 38.8 µg/ml for the healthy group, 134 ± 52.0 µg/ml for the staphylococcal meningitis group, and 195 ± 74.3 µg/ml for the *E. coli* meningitis group.

The mean *C*ₘₐₓ in CSF was 1.06 ± 0.85 µg/ml for the healthy group at 75 min after intravenous infusion, 4.51 ± 3.95 µg/ml for the staphylococcal meningitis group after 30 min, and 8.58 ± 3.85 µg/ml for the *E. coli* meningitis group after 30 min.

On the basis of these results, the half-lives (*t*₁/₂) of cefuzoname in serum and CSF were calculated with the least-square method. Also, the areas under the concentration-time curves (AUCs) at 15 to 60, 15 to 120, and 15 to 180 min were calculated (Table 2).

The *C*ₘₐₓ in the sera of the staphylococcal meningitis group was lower than that of the other two groups. Statisti-
tically, there was no significant difference between the three groups, and the differences might be ascribable to individual variation.

No significant difference was observed in CSF Cmax between the healthy and staphylococcal meningitis groups, but in the staphylococcal meningitis group the AUC for CSF vs. that for serum (AUC CSF/serum) at 15 to 60, 15 to 120, and 15 to 180 min after administration was significantly higher than that in the healthy group. Between the E. coli meningitis group and the healthy group there were significant differences in both CSF Cmax and AUC CSF/serum. In comparison with the staphylococcal meningitis group, the E. coli meningitis group showed greater values of CSF Cmax and AUC CSF/serum, but the differences were not significant.

In many rabbits of the E. coli meningitis group the t1/2 in CSF was lengthy, showing a significant difference in mean values between this group and the staphylococcal meningitis group. However, no significant difference was observed with respect to the t1/2 between the E. coli meningitis group and the healthy group, which fact was thought to be attributable to a persistent low concentration in the CSF of one rabbit in the healthy group, the t1/2 of which was as long as 163 min.

### DISCUSSION

The results of the study on cefuzoname in rabbits with staphylococcal meningitis were compared with those of other β-lactam agents with 5-min intravenous infusion (Table 3) (2–9, 12–24, 26). The Cmax and AUC CSF/serum of cefuzoname were similar to those of aztreonam, cefmenoxime and cefpirome and obviously superior to those of penicillin G, cefotiam, cefotetan, and cefudolin, which places cefuzoname among the middle ranks of various β-lactam agents as far as penetration is concerned.

Thus, it is probable that cefuzoname is effective on meningitis induced by bacteria against which the compound has an activity similar to that of penicillin G. Against both Streptococcus pneumoniae and Streptococcus pyogenes the MIC for 90% of the strains tested (MIC90) of cefuzoname is 0.012 μg/ml (Hikida et al., 24th ICAAC), whereas the MIC90 of penicillin G is less than 0.012 μg/ml against S. pneumoniae and 0.39 μg/ml against Streptococcus agalactiae (1). According to reports at the Pediatric Society conference in Japan, the concentrations of cefuzoname in CSF in pediatric patients with purulent meningitis are 3 to 6 μg/ml in many cases at the early stage of the disease (personal communication). It is also emphasized (25, 27, 28) that, even if the concentration in CSF reaches the in vitro MBC, the bactericidal potency is not sufficient in vivo. Opinions vary as to how many times the in vitro MBC is necessary for bactericidal activity in vivo; however, on the assumption that the bactericidal potency required for a living body is at least 10-fold the in vitro MBC, and taking the above-mentioned clinical reports on CSF concentrations into account, it is thought that cefuzoname can be used safely for meningitis caused by pathogens for which the MBC for 90% of strains tested (MBC90) of this compound is below 0.3 μg/ml. Because the MIC and MBC of cefuzoname are nearly the same (M. Hikida, M. Inoue, and S. Mitsuhashi, Abstr. 14th Int. Congr. Chemother., Kyoto, Japan, p.49-8, 1985), data on bacterial species for which the MIC90 of cefuzoname is below 0.3 μg/ml are, as mentioned below, taken from a report on the results of susceptibility measurements of clinical isolates in Japan (Y. Shigeno, A. Tomonaga, Y. Suzukiyama, K. Yamaguchi, M. Hirota, A. Saito, and K. Harai, Abstr., 14th Int. Congr. Chemother., Kyoto, Japan, pp.49-11, 1985). Included are: S. pneumoniae (0.1 μg/ml), S. pyogenes (0.013 μg/ml), E. coli (0.2 μg/ml), and Haemophilus influenzae (0.05 μg/ml). Also, for Klebsiella pneumoniae and Proteus mirabilis the MIC90 is 0.39 μg/ml, a little higher, but close to 0.3 μg/ml.

There are no substantial test data on S. agalactiae, but our
study on two strains isolated from patients with meningitis showed that the MICs of ceftazidime were 0.05 and 0.025 µg/ml, whereas the MBC was 0.05 µg/ml for both strains. The MIC of ampicillin was 0.1 µg/ml for both strains, and the MBCs were 0.1 and 0.2 µg/ml. Since S. agalactiae, E. coli, H. influenzae, and S. pneumoniae are the principal causative bacteria of pediatric purulent meningitis, and more than half of the total cases whose causative bacteria are identified involve these pathogens (10), the compound is considered to be usable for the therapy of meningitis, although further studies on the susceptibility of S. agalactiae to ceftuzidine in a larger number of strains are required. The antibacterial activity of ceftuzidine on Neisseria meningitidis has not yet been measured. In Japan, meningitis caused by this etiological agent is rarely encountered (10), but it has been considered necessary to study the effect of this compound on the meningitis which is common in other regions of the world. Although activity against staphylococci is claimed to be a strong point of ceftuzidine, the MIC 25 µg/ml against S. aureus and Staphylococcus epidermidis, and the percentage of inhibition of bacterial growth below 0.3 µg/ml is 10% for S. aureus and 25% for S. epidermidis; thus, efficacy appears to be limited. Even so, this compound is still superior to other broad-spectrum cephalosporins. Since the current therapeutic status is such that adequate antibiotics for staphylococcal meningitis are lacking, this antibiotic can be considered beneficial if it is safely usable for meningitis, even if the applicable cases are limited.

In sum, the results of the present study suggest that extensive clinical investigations on the penetration of ceftuzidine into the CSF of patients with meningitis are worth conducting.

LITERATURE CITED


