Nafcillin Entry into Human Cerebrospinal Fluid

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The entry of nafcillin into the cerebrospinal fluid (CSF) of humans was studied in the absence of meningeal inflammation. Twenty studies were performed in 18 patients receiving 40 mg of sodium nafcillin per kg intravenously over 30 min. The CSF specimens were obtained at 1, 2, 3, and 4 h postinfusion, and sera were obtained at 5 min and 1, 2, 3, and 4 h. Nafcillin was uniformly detected in the lumbar CSF at 1 h, peaked at 2 h postinfusion, and was still detectable in the CSF of three of four patients studied at 4 h.

Meningitis caused by Staphylococcus aureus is relatively rare, but presents a major therapeutic problem because of a mortality rate approximating 50% (1). Currently the semisynthetic penicillinase-resistant penicillins are the drugs of choice for the therapy of staphylococcal meningitis (1, 4). However, minimal data exist regarding the passage of these agents into the cerebrospinal fluid (CSF) of humans (4). As a result, very large doses of these antimicrobials are empirically recommended for treatment of staphylococcal meningitis (1).

This paper reports the results of a prospective study undertaken to define the degree of entry of a particular penicillinase-resistant penicillin, sodium nafcillin, into the CSF of patients without meningeal inflammation.

MATERIALS AND METHODS

Patients. The study group was composed of patients admitted to the Medical Oncology ward who underwent lumbar puncture as part of a staging evaluation for malignancy. The subjects were eligible for the study if they were not receiving antimicrobial therapy and had no history of penicillin allergy. After informed consent was obtained, the patients were skin tested for sensitivity to nafcillin before intravenous infusion of the drug. Patients with a clinical history of penicillin allergy were not administered nafcillin, but a portion of their CSF specimen was obtained for assay of intrinsic antimicrobial activity. Twenty studies were performed on 18 patients. Six patients were women and 12 were men. They ranged in age from 36 to 69 years, with a mean age of 57.7 years. Seventeen patients had carcinoma of the lung, and one patient had mycosis fungoides.

Method of study. On the day the lumbar puncture was performed, intravenous access was obtained with a 20-gauge butterfly needle and normal saline. A prestudy blood sample was drawn to assay serum intrinsic antimicrobial activity. Sodium nafcillin, 40 mg/kg in 100 ml of normal saline, was administered by a constant-infusion pump over a 30-min period, after which the intravenous line was removed. The total dose of drug administered ranged from 1.8 to 3.8 g, with an average dose of 2.5 g. A single lumbar puncture was performed on each patient at time intervals varying from 1 to 4 h after the infusion of drug had ceased, and simultaneous CSF and blood specimens were obtained for bioassay of nafcillin concentration. Several patients permitted more than one blood sample to be collected during the 4-h postinfusion period. CSF specimens were obtained at 1, 2, 3, or 4 h after cessation of the nafcillin infusion. Eight CSF specimens were obtained from patients who did not receive nafcillin. Serum specimens were obtained before nafcillin from all patients and 5 min and/or 1, 2, 3, or 4 h after the infusion ended. Table 1 shows the temporal distribution of the CSF and serum specimens.

All CSF specimens were plated on Columbia sheep blood agar, Fildes peptic digest of blood agar, and MacConkey agar in addition to being inoculated into thioglycolate and Trypticase soy broths. The agar plates were placed in a 10% CO2 atmosphere and examined after 24 and 48 h of incubation. In addition, the leukocyte count with differential cell count and the glucose and protein concentrations were determined for all CSF specimens. The concentration of glucose in the blood at the time of the lumbar puncture was also measured. All specimens were kept frozen at -20°C until assayed.

Antimicrobial assay. Bioassay of CSF and serum nafcillin concentrations were performed using the basic method of Grove and Randall by Wyeth Laboratories, Philadelphia, Pa. (3). CSFs were diluted with pH 7.0 phosphate buffer and assayed, using Staphylococcus aureus ATCC 6538P as the test microorganism. Sera were diluted in pooled antibiotic-free human serum and assayed, using Sarcina lutea ATCC 9341 as the test microorganism. All specimens from a given patient were assayed simultaneously.

RESULTS

CSF could not be obtained from one patient, and another patient had hemorrhagic CSF.
TABLE 1. Concentration of nafcillin in the cerebrospinal fluid (CSF) and serum of patients before infusion and after intravenous administration of 40 mg/kg

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>CSF</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of specimens*</td>
<td>Range (µg/ml)</td>
</tr>
<tr>
<td>Preinfusion</td>
<td>8</td>
<td>0.00-0.00</td>
</tr>
<tr>
<td>Postinfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>7</td>
<td>0.02-0.09</td>
</tr>
<tr>
<td>120</td>
<td>4</td>
<td>0.03-0.17</td>
</tr>
<tr>
<td>180</td>
<td>3</td>
<td>0.06-0.12</td>
</tr>
<tr>
<td>240</td>
<td>4</td>
<td>0.00-0.07</td>
</tr>
</tbody>
</table>

* One specimen excluded due to presence of blood.
* In some patients, more than one serum specimen was obtained for assay.

which precluded CSF studies; however, serum studies were carried out for both subjects.

None of the CSF specimens showed changes of meningeal inflammation as shown by the results of biochemical determinations and cell counts. The glucose concentration in the CSF ranged from 20 to 88 mg/dl. It was equal to or greater than 50 mg/dl in all but two CSF specimens, which had values of 20 and 38 mg/dl. The CSF/serum glucose ratio ranged from 0.16 to 0.85 and was greater than 0.4 in all but one case. The CSF protein concentration ranged from 10 to 96 mg/dl and exceeded 43 mg/dl in five cases; the latter values were 50, 60, 69, 94, and 96 mg/dl. The CSF leukocyte count was always 4 cells/mm² or less. All CSF specimens were sterile. None of the patients were found to have central nervous system metastases. The serum creatinine was 1.4 mg/dl or less in all subjects, and serum bilirubin concentration did not exceed 1.1 mg/dl.

Five minutes after the end of infusion, the mean serum nafcillin concentration for six studies was 103 µg/ml (Table 1). This concentration fell to a mean of 2.7 µg/ml by 4 h. The mean CSF concentration detectable at 1 h postinfusion was 0.05 µg/ml. A mean peak CSF nafcillin concentration of 0.12 µg/ml occurred 2 h after the end of infusion, and the 4-hour mean concentration reached a nadir of 0.03 µg/ml. The eight CSF specimens from the control patients receiving no drug, and the 20 preinfusion serum samples showed no detectable antimicrobial activity. The relationships between serum and CSF nafcillin concentrations are depicted in Fig. 1.

Fig. 1. Serum and cerebrospinal fluid concentration of nafcillin in patients without meningeal inflammation after a single 40-mg/kg intravenous dose.

DISCUSSION

The results of the study indicate that sodium nafcillin enters the CSF of humans in detectable amounts even in the absence of meningeal inflammation. The drug was uniformly present at the first time interval of 1 h in the lumbar CSF of all seven patients studied. The mean peak CSF nafcillin concentration of 0.12 µg/ml occurred at 2 h after the infusion, and nafcillin...
was still detectable in the CSF of three of four patients studied at 4 h after the end of drug administration.

No prior reports describing the entry of nafcillin into the CSF of humans in the absence of meningeal inflammation have been published. However, Ruiz and Warner have reported serum and CSF nafcillin levels in a patient with staphylococcal meningitis (4). In their patient, who received nafcillin, 200 mg/kg per 24 h, administered as a 3.0-g intravenous bolus every 4 h, the 5- and 60-min postinfusion serum levels of 104 and 26 μg/ml, respectively, closely approximated the results of the current study. Lumbar CSF assay for nafcillin from the same patient revealed no detectable drug at 5 min after the dose. In the current study, nafcillin was present in the CSF in low but detectable concentrations at 4 h after a single dose, 1.8 to 2.4 g, in three of four patients. In contrast, the CSF nafcillin concentration 45 min after the dose in the meningitis patient was 190 times greater than the mean 1 h postdose CSF concentration of 0.05 μg/ml in the patients currently reported.

The dose of antimicrobials used for both prophylaxis and therapy of staphylococcal meningitis is largely empiric (1). Previous studies of the susceptibility of penicillinase-producing staphylococci to nafcillin have revealed minimum inhibitory concentrations ranging from 0.1 to 1.6 μg/ml, with medians of 0.4 to 0.8 μg/ml (2, 5). The concentration of nafcillin in the CSF equaled or exceeded 0.1 μg/ml in five of the patients reported here, and the highest concentration achieved was 0.17 μg/ml. This information and the data reported previously in a patient with meningitis support the concept that large doses of nafcillin are appropriate when used for both prophylaxis and therapy of staphylococcal meningitis.

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LITERATURE CITED