Nafcillin Treatment of Staphylococcus aureus Meningitis

DANIEL E. RUIZ1 AND JOHN F. WARNER*

The Division of Infectious Diseases, The Ohio State University College of Medicine, Columbus, Ohio 43210

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Serial serum and cerebrospinal fluid nafcillin concentrations were determined in a patient successfully treated with nafcillin (200 mg/kg per day) for Staphylococcus aureus bacteremia and meningitis. Nafcillin and methicillin cerebrospinal fluid concentrations were compared.

Little published information is available concerning the efficacy of penicillinase-resistant semisynthetic penicillin derivatives in the treatment of bacterial meningitis. Nafcillin is considered by many physicians to be the drug of choice in the treatment of serious penicillin-resistant staphylococcal infections (3), yet there are no data available on the penetration of this drug into the cerebrospinal fluid (CSF) of humans. This paper reports a case of penicillin-resistant Staphylococcus aureus bacteremia and meningitis successfully treated with intravenous nafcillin. Serum and CSF nafcillin levels were determined in this patient.

A 69-year-old, white diabetic male was transferred to Ohio State University Hospital because of recurrent S. aureus bacteremia. On admission, he complained of pain in his right hip. An examination revealed a temperature of 40°C, nuchal rigidity, a fluctuant mass (6 cm in diameter) just to the left of the manubrium, and bilateral, lower-extremity weakness and hyporeflexia. A lumbar puncture yielded purulent CSF, which on analysis was found to contain 1,300 leukocytes per mm³, with 86% polymorphonuclear leukocytes, 5% lymphocytes, and 9% monocytes. There were 60 erythrocytes per mm³. The CSF sugar and protein were 137 and 272 mg/dl, respectively. The blood sugar was 330 mg/dl. A gram-stained smear of pus aspirated from the above-mentioned fluctuant mass revealed gram-positive cocci in clusters. Cultures of blood, CSF, and pus grew S. aureus that was resistant to benzylpenicillin. After cultures were obtained, treatment was begun with 3 g of nafcillin intravenously every 4 h (200 mg/kg per 24 h).

On day 2 of hospitalization, lumbar puncture was repeated. The spinal needle was left in place, and CSF and blood samples were obtained immediately before and 5, 15, 30, and 45 min after intravenous infusion of 3 g of nafcillin over a period of 5 min. A blood sample, but no CSF sample, was obtained 60 min after the infusion of nafcillin.

On day 3 of hospitalization, the blood cultures of the patient were found to contain Escherichia sp., and gentamicin therapy was begun. Parenteral gentamicin and/or ampicillin therapy were continued through day 40 of hospitalization. The source of the mixed bacteremia was osteomyelitis of the right sacroiliac area.

Intravenous nafcillin therapy (200 mg/kg per 24 h) was continued through day 19 of hospitalization. At this time, CSF was obtained by lumbar puncture. The fluid contained 75 erythrocytes and 15 leukocytes per mm³. The leukocytes were all lymphocytes. The CSF protein and sugar were 85 and 112 mg/dl, respectively. Gram stain and culture were negative. Antistaphylococcal therapy was continued from day 19 through day 40 of hospitalization, first with reduced dosages of parenteral nafcillin and then with oral dicloxacillin. Other than a transient, generalized urticarial rash, which occurred on day 10 of hospitalization, no adverse drug effect was observed.

Blood and CSF nafcillin levels were determined by plate agar dilution, utilizing Bacillus subtilis as the assay organism. The assay method has been published elsewhere (1, 7).

Table 1 shows the concentrations of nafcillin in the serum and CSF samples obtained from the patient at the indicated intervals.

The minimal inhibitory concentration of nafcillin for the infecting staphylococcus was 0.25 μg/ml, and the organism was eradicated with the resulting cure of the patient.

In this case, the efficacy of nafcillin for the treatment of S. aureus meningitis is clearly demonstrated. An important aspect of such therapy is the need to produce very high serum levels of nafcillin in order to produce adequate concentrations of the drug in the CSF. The highest measured concentrations in the CSF occurred approximately 40 min after peak serum concentrations, and the former levels were only 9% of the latter (Table 1). Higher CSF

1 Present address: The Frederick Smith Clinic, 1040 Delaware Avenue, Marion, Ohio 43302.
concentrations of the drug may have evolved after 45 min, but further samples could not be obtained due to discomfort of the patient. However, the concentration of 9.5 μg/ml is many times the usual minimal inhibitory concentration of nafcillin for S. aureus. Klein and Finland (4) found the average minimal inhibitory concentration of nafcillin for penicillinase-producing S. aureus to be 0.6 μg/ml, with a range of 0.4 to 0.8 μg/ml.

Methicillin has been found to reach the CSF of normal humans in only very small concentrations (2, 5, 6). Oppenheimer et al. (5) studied patients with acute bacterial meningitis and found CSF methicillin concentrations of 1.70, 1.30, and 1.66 μg/ml at unspecified times after the intravenous administration of 2 g of the drug. Douthwaite et al. (2) found a CSF methicillin level of 2.8 μg/ml 1 h after administering an unspecified amount of the drug via an unspecified route to a patient with meningitis. Such CSF levels appear inadequate for the reliable therapy of meningitis due to penicillin-resistant S. aureus, as the mean minimal inhibitory concentration of methicillin for these organisms is 3.1 μg/ml, with a range of 0.8 to 6.3 μg/ml (4).

This case report supports the impression of other workers (3) that nafcillin is probably the drug of choice in the treatment of penicillin-resistant S. aureus meningitis.

We wish to gratefully acknowledge the excellent technical assistance of Jean Barnihan.

LITERATURE CITED

### Table 1. Serum and CSF nafcillin concentrations

<table>
<thead>
<tr>
<th>Time of sampling</th>
<th>Nafcillin concentrations (μg/ml)</th>
<th>Serum</th>
<th>CSF</th>
</tr>
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<tbody>
<tr>
<td>Before infusion</td>
<td>&lt;1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Postinfusion</td>
<td>5 min</td>
<td>104</td>
<td>0</td>
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<tr>
<td></td>
<td>15 min</td>
<td>75</td>
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<td>30 min</td>
<td>32</td>
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<td>45 min</td>
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<td>60 min</td>
<td>26</td>
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