Unusually High Occurrence of Drug Reactions with Nafcillin

BEHNAM ZAKHIREH, M.D., AND RICHARD K. ROOT, M.D.

Infectious Disease Section, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

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Five patients seen during a two-month period who developed untoward systemic reactions following high dose intravenous administration of nafcillin are described. Recovery was complete upon discontinuation of the drug. The clustering of these cases and the high incidence (5 of 5) of side effects are highly unusual, and suggest that the frequency of nafcillin reactions might be higher than previously suspected.

It is assumed that all penicillinase-resistant semi-synthetic penicillins are equally effective in treating infections caused by Staphylococcus aureus [1,2]. Little is known, however, about the relative toxicities of these antibiotics. Of the major side effects, rash, urticaria, fever, allergic interstitial nephritis, hepatic toxicity, and hematologic toxicity in the form of reversible granulocytopenia have been commented upon in the literature [3–10].

Nafcillin, 6-(2-ethoxy-1-naphthalmido) penicillanic acid, has been preferred by some clinicians over methicillin and oxacillin, because its use may be associated with a lower incidence of side effects, particularly nephropathy [11]. Furthermore, in one study nafcillin offered better synergistic activity than other penicillinase-resistant penicillins with an aminoglycoside when tested against the enterococci [12].

This report describes an unusually high occurrence of untoward reactions due to nafcillin observed by us at Yale-New Haven Hospital. During the months of July and August of 1976, five patients, four of whom were seen and followed by the Infectious Disease Section, received high dose intravenous nafcillin for proven or presumed staphylococcal infections. All five subsequently developed various drug reactions, necessitating discontinuation of nafcillin in four of the patients. To the best of our knowledge, no other patient received nafcillin at our institution during this period.

CASE REPORTS

Case 1

A 22-year-old male with chronic non-union of a left tibial fracture underwent open reduction with internal fixation and bone grafting of the left tibia at Yale-New Haven Hospital. Twenty-five days later he was re-admitted to the hospital with a 3-day history of fever, rigors, and local pain and swelling at the site of operation. There was no history of trauma, or allergies. On admission to the hospital the patient had a...
temperature of 101.6° F, a pulse of 108/min, respirations of 18/min, and a BP of 130/80 mm Hg. On physical exam the surgical wound of the left leg was erythematous, swollen, and tender. Tender left inguinal adenopathy was also noted. The remainder of the exam was negative. Admission laboratory findings revealed an erythrocyte sedimentation rate of 57 mm/hr, a hemoglobin of 11.5 g/dl, and a hematocrit of 34.7%. The WBC count was 10,300/mm³, with 72% segmented neutrophils, 6% bands, 17% lymphocytes, and 6% monocytes. Urinalysis, BUN, creatinin, electrolytes, and the results of the liver function studies were normal. Cultures of the wound aspirate as well as cultures obtained during surgical debridement yielded *S. aureus*. Intravenous oxacillin in the dosage of 1 g every 6 hours was begun, and two days later was changed to intravenous nafcillin 2 g, every 6 hours. The wound infection responded satisfactorily to treatment, and the temperature returned to normal. On the twentieth day of nafcillin therapy, the WBC count was 4,300/mm³, with 38% neutrophils, 21% bands, 25% lymphocytes, 5% monocytes, and 7% eosinophils. On the twenty-first day of nafcillin therapy, he developed a fever of 102° F, and by the twenty-second day a confluent, erythematous, maculopapular rash appeared with a fever of 103° F. The WBC count was 935/mm³, with 5% segmented neutrophils, 2% bands, 57% lymphocytes, 29% monocytes, and 6% eosinophils. Nafcillin was discontinued and during the following five days the WBC count rose to 6,100/mm³, with 34% neutrophils, 10% bands, 26% lymphocytes, 10% monocytes, and 16% eosinophils. The fever and rash also disappeared. The results of urinalysis, renal, and liver function studies remained normal. The patient received several other medications at the time of his reaction, none of which were stopped while he recovered successfully. Two weeks after cessation of nafcillin, at the time of discharge, the patient was asymptomatic, and had a WBC count of 9,500/mm³, with 59% neutrophil, 2% bands, 29% lymphocytes, 8% monocytes, and 2% eosinophils.

**Case 2**

A 22-year-old male was seen at Yale-New Haven Hospital Emergency Room with a 10-day history of right tibial pain and swelling, and 3 days of fever, and night sweats. There was no history of trauma or allergies. Physical exam revealed a temperature of 99.2° F orally, a pulse of 72/min, respirations 18/min, and a BP of 130/80 mm Hg. Edema, increased warmth, tenderness along the mid-shaft of the right tibia, and a positive Homan's sign were noted. The remainder of exam was negative. The erythrocyte sedimentation rate was 38 mm/hr, the hemoglobin 14 g/dl, and the hematocrit 40.5%. The WBC count was 9,600/mm³, with 72% segmented neutrophils, 15% bands, 7% lymphocytes, and 6% monocytes. Films of the right tibia and a venographic study of the right leg were negative. Two days later a ⁹⁹Tc-bone scan showed diffuse increased uptake of the right tibia, and the patient was admitted to the hospital. Surgical exploration of the right tibia revealed a “roughened” periosteum, and necrotic bone; however, no gross pus or tumor was noted. The surgical biopsy did not show definite evidence of infection or tumor. All of the operative cultures were negative except for one specimen from the medullary cavity which yielded a few *Staph. epidermidis*. It was felt that the patient's presentation was most compatible with osteomyelitis, and therapy with intravenous cephalothin at a dosage of 1 g every 4 hours was begun postoperatively. This was changed three days later to intravenous nafcillin, 2 g every 6 hours. On the thirteenth day of nafcillin therapy the WBC count was 7,000/mm³, with 66% neutrophils, 5% bands, 10% lymphocytes, 10% monocytes, and 4% eosinophils. On the seventeenth day of nafcillin therapy, the patient developed a pruritic, maculopapular rash on the trunk.
and shoulders. The WBC count was 3,700/mm$^3$, with 30% segmented neutrophils, 10% bands, 38% lymphocytes, 11% monocytes, and 11% eosinophils. Urinalysis, renal, and liver function tests were normal. Nafcillin was stopped on the seventeenth day of therapy, and intravenous cephalothin, 1 g every 4 hours was started. No other medications were stopped. During the following three days the WBC count rose to 5,100/mm$^3$, with 65% neutrophils, 3% bands, 20% lymphocytes, 10% monocytes, and 2% eosinophils. The rash improved within one week. Several months after discharge the patient was asymptomatic, and had a normal erythrocyte sedimentation rate and radiographic evidence of healing of the right tibia.

**Case 3**

A 53-year-old man underwent exploration of the right knee with removal of the torn medial meniscus at Yale-New Haven Hospital. He was discharged 2 days after the operation. Three days later he fell, and sustained a flexion injury to the right knee, causing dehiscence of the inferior pole of the surgical wound, and a small amount of drainage. The next day he was seen in the Orthopedic Clinic, where the wound was aspirated, and phenoxybenzyl penicillin, 250 mg, four times a day was started. During the subsequent week, pain and swelling of the right knee became worse, and after a culture of the wound yielded *S. aureus* resistant to penicillin, the patient was admitted to the hospital. On admission he had a temperature of 98.8° F orally, a pulse of 90/min, respirations 14/min, and a BP of 120/80 mm Hg. Physical exam revealed a partially open right knee wound, with swelling, tenderness, and surrounding erythema. The remainder of the exam was negative. Admission laboratory showed a hemoglobin of 15.1 g/dl, a hematocrit of 44.1%, and a WBC count of 8,500/mm$^3$, with 67% neutrophils, 3% bands, 20% lymphocytes, 8% monocytes, 1% basophils, and 1% eosinophils. An X-ray film of the knee showed only soft tissue swelling. Urinalysis, electrolytes, BUN, creatinin and the liver function studies were normal. Gram stain and culture of the wound revealed *S. aureus*. Treatment with intravenous nafcillin, at the dosage of 2 g every 6 hours, was started, with rapid improvement of the wound infection. On the eighth day of nafcillin therapy the patient developed a fever of 103° F, and a WBC count of 7,800/mm$^3$, with 60% neutrophils, 7% bands, 11% lymphocytes, 12% monocytes, and 8% eosinophils. Fever persisted and on the twelfth day of nafcillin therapy a pruritic, erythematosus, maculopapular rash developed on the extremities and chest, which soon became generalized. The WBC count was unchanged, and the results of urinalysis, renal and hepatic function tests remained normal. Nafcillin was stopped, but all of his other medications were continued. Because of persistence of severe, symptomatic rash, unresponsive to diphenhydramine, treatment with hydrocortisone 100 mg intravenously, followed by 30 mg of prednisone/day, for two days was given with rapid improvement of the rash and return of the temperature to normal. Three days later, cephalaxin 500 mg, then subsequently 1 g, four times/day was begun. During the following week the wound improved considerably and the patient remained asymptomatic. He was discharged on cephalaxin 4 g/day.

**Case 4**

A 19-year-old male was admitted to another hospital with a 3-month history of progressive low back pain, and the recent onset of night sweats. There was no history of trauma, allergy, or neurologic deficits. Physical exam showed marked paravertebral muscle spasm, local tenderness of the lower lumbar spine, and severe limitation
of spine movements. Tomographic examination of the lumbar spine was compatible with osteomyelitis of the L₃ vertebra, with destruction of the L₃–₄ disc space. The patient was subsequently transferred to Yale-New Haven Hospital. Physical exam was unchanged. The admission laboratory data showed an erythrocyte sedimentation rate of 47 mm/hr, a hemoglobin of 13.1 g/dl, a hematocrit of 39.8%, and a WBC count of 11,000/mm³, with 76% segmented neutrophils, 2% bands, 14% lymphocytes, 6% monocytes, and 1% eosinophils. The remainder of laboratory exams were within normal limits. Surgical exploration confirmed the diagnosis of osteomyelitis. All of the bone cultures and one blood culture yielded *S. aureus*. Post operatively, therapy with intravenous nafcillin, 2 g every 6 hours, was started. On the eighth day of nafcillin therapy a pruritic, maculopapular rash appeared on the abdomen and chest, and rapidly involved the extremities. The WBC count was 12,800/mm³, with 74% neutrophils, 13% lymphocytes, 6% monocytes, and 7% eosinophils. All other laboratory results, including the urinalysis, BUN, and liver function tests were normal. Nafcillin was stopped, and the rash and eosinophilia improved during the subsequent 3 days. None of the patient's other medications were stopped. Therapy with intravenous cephalothin, 2 g every 6 hours was then started, and continued for a total of 30 days. At the time of discharge, the erythrocyte sedimentation was normal, and the WBC count was 8,600/mm³, with 70% neutrophils, 5% bands, 16% lymphocytes, 6% monocytes, 2% basophils, and 1% eosinophils.

**Case 5**

A 60-year-old male was admitted to Yale-New Haven Hospital after he fell and sustained a fracture of the mid-shaft of the left femur. On admission, physical exam was negative, except for a BP of 152/94 mm Hg, and the pertinent findings associated with the femoral fracture. The admission laboratory data revealed a hemoglobin of 14.6 g/dl, a hematocrit of 43.3%, and a WBC count of 8,800/mm³, with 71% neutrophils, 4% bands, 19% lymphocytes and 6% monocytes. Hydrochlorothiazide, 25 mg/day, was given for hypertension, but stopped after 2 weeks. Treatment with traction was employed initially, and 3 weeks after the admission he underwent internal fixation of the left femur with placement of a Kuntschner rod. Perioperative cephalothin, 1 g every 4 hours, was given for a total of 10 doses. On the twelfth postoperative day the patient developed fever of 102°F, and evidence of the surgical wound infection. Wound cultures yielded an abundant growth of *S. aureus*. Treatment with intravenous cephalothin was restarted. After two days this was changed to oxacillin and subsequently to intravenous nafcillin, at a dosage of 2 g every 6 hours. In addition, surgical debridement of the wound was carried on. He responded well to the treatment, with gradual clearing of the wound infection. However, CBC's on the thirteenth to sixteenth day of nafcillin therapy showed a persistent eosinophilia of 11%. There was no rash, fever, renal or hepatic abnormalities. Nafcillin was stopped after 21 days of therapy, and the patient was discharged on oral dicoxacillin 500 mg, four times/day. The only other medications that the patient had received within one week of development of the eosinophilia were meperidin, flurazepam, and hydroxyzine. No further follow-up blood counts were available at the time of preparation of this manuscript.

**DISCUSSION**

Adverse reactions to nafcillin have been infrequently reported in the past. Bone marrow examination in two previous case studies of nafcillin-induced granulocytopenia demonstrated a maturation arrest of the myeloid series at the myelocyte stage,
without depression of the erythroid or the megakaryocytic series [9,10]. Nafcillin has also been reported to cause interstitial nephritis in a patient with a previous history of methicillin-induced nephropathy [8]. In a recent study comparing nafcillin and methicillin in treatment of patients with serious staphylococcal infections, nafcillin was associated with a substantially lower incidence of side effects. In particular, no instances of nephropathy were observed in the 29 patients treated with nafcillin, and only four patients developed reactions to the drug. One patient had only fever and rash, two developed granulocytopenia, and one patient treated with the highest daily dose of nafcillin (12 grams) developed granulocytopenia associated with fever and rash [11]. In contrast, in another as yet not completed study comparing nafcillin versus combination of nafcillin and gentamicin in treatment of severe staphylococcal infections, reaction rates (eosinophilia, rash, and neutropenia) of over 50% have been observed with combined regimen. Nafcillin alone has been associated with adverse reactions in nearly 30% of cases (Merle Sande, M.D., personal communication). In our series of five patients receiving intravenous nafcillin, all five developed untoward reactions. Eosinophilia was seen in all, and maculopapular rash in four patients. Two had both fever and a reversible granulocytopenia. No evidence of nephropathy or liver damage was observed in any of the patients (Refer to Table 1.) All of the four patients who had adequate follow-up experienced complete recovery upon discontinuation of nafcillin, and did not exhibit cross-reactive side effects with cephalosporins as the substitute therapy. None of our patients had a past history of allergic reactions to the penicillins or other drugs. The nafcillin used during this period came from different lots, was freshly prepared, and administered by the standard "piggy back" intravenous infusion in isotonic saline, or 5% dextrose solution. Thus the possibility that the reactions were due to the contamination of a single lot of the drug is unlikely. Furthermore the concurrent use of other medications in these patients was minimal, and none were stopped when the adverse reactions appeared.

Fever, rash, and pruritus occurring on penicillin therapy have been attributed to hypersensitivity reactions. Likewise, the interstitial nephritis due to penicillin and its homologues (including nafcillin) is thought to represent a dose-related hypersensitivity reaction [8,13]. One group of investigators demonstrated antitubular basement membrane antibodies in methicillin-associated nephritis [14]. The mechanism of selective granulocytopenia by penicillin homologues has been the source of considerable speculation. Most patients, as did ours, appear to develop this complication at about 3 weeks into treatment by these agents [7,9–11]. Both a direct toxic effect on the granulocytic series [15], and an antibody-mediated hypersensitivity reaction [7,9] have been suggested. In a recent study [16] antineutrophil antibodies were demonstrated in the sera of 2 patients with nafcillin, and one patient with oxacillin-induced granulocytopenia. The authors suggested that these drugs attach to the cell surface where they function as haptens, with subsequent antibody attachment. The opsonized neutrophils are then sequestered and phagocytized by macrophages of the reticuloendothelial organs. The association of eosinophilia and rash observed in our patients with granulocytopenia favors a hypersensitivity reaction. However, further studies are needed to elucidate the mechanism(s) of granulocytopenia due to penicillin homologues.

These cases are brought to the attention of readers to emphasize the possibility that when larger series of patients are treated with nafcillin, reaction rates will approach those reported with other semi-synthetic, penicillinase-resistant penicillins. Careful observation of patients receiving large doses of intravenous nafcillin (or other penicillinase-resistant penicillins) for the development of hypersensitivity reactions,
| Pt. | Sex and Age | Diagnosis            | Nafcillin dose and Duration of Rx | Untoward Reactions* |
|-----|-------------|----------------------|-----------------------------------|---------------------|
|     |             |                      | Rash | Eosinophilia (%) | Fever<sup>b</sup> | Leukopenia<sup>c</sup> | Outcome            |
| MG  | M 23        | Osteomyelitis        | 2g.Q6H 21 days                    | 22 | 20 (16%) | 21 | 22 | Complete recovery |
| JM  | M 22        | Presumed osteomyelitis | 2g.Q6H 17 days                    | 17 | 13 (14%) | None | 17 | Complete recovery |
| FH  | M 53        | Wound infection      | 2g.Q6H 12 days                    | 12 | 8 (8%)  | 8    | None | Complete recovery |
| MM  | M 19        | Osteomyelitis        | 2g.Q6H 8 days                     | 8  | 8 (7%)  | None | None | Complete recovery |
| WM  | M 60        | Wound infection      | 2g.Q6H 23 days                    | None | 13 (11%) | None | None | ?<sup>d</sup> |

<sup>*Numbers indicate the day of therapy a particular reaction occurred.</sup>
<sup><sup>Numbers indicate the lowest count, number followed in parenthesis indicates the lowest absolute neutrophils count. Leukopenia is defined as a WBC count of < 4,000/mm<sup>3</sup>, and neutropenia as an absolute neutrophil (segmented, and bands) of < 1,500/mm<sup>3</sup>.</sup></sup>
and frequent monitoring of blood counts with differentials, as well as renal and hepatic functions are recommended, particularly after 2 weeks of treatment. If isolated neutropenia (neutrophil count < 1,800/mm³) appears without other manifestations of hypersensitivity then the dose should be lowered and the patient followed closely for other complications. Should these appear at any time or the granulocyte count fall below 1,000/mm³ the drug should be stopped. Vancomycin or a cephalosporin may provide suitable alternative treatment for staphylococcal infections should such side effects be observed.

REFERENCES

1. Martin CM: Clinical status of nafcillin. Antimicrob Agents Chemother 4:285, 1964
2. Gilbert DN, Sanford JP: Methicillin: Critical appraisal after a decade of experience. Med Clin N Amer 54:1113, 1970
3. McElfresh AE, Huang NN: Bone marrow depression from the administration of methicillin. N Engl J Med 266:246, 1962
4. Levitt BH, Gottlieb J, Rosenberg IR, et al: Bone marrow depression due to methicillin, a semi-synthetic penicillin. Clin Pharmacol Ther 5:301, 1964
5. Dismukes WE: Oxacillin-induced hepatic dysfunction. J Amer Med Assoc 226:861, 1973
6. Freedman MA: Oxacillin-apparent hematologic and hepatic toxicity. Rocky Mt Med J 62:34, 1965
7. Ahern MJ, Hicks JE, Andriole VT: Neutropenia during high dose intravenous oxacillin therapy. Yale J Biol Med 49:351, 1976
8. Parry MF, Ball WD, Conte JE, Jr, et al: Nafcillin nephritis. J Amer Med Assoc 225:178, 1973
9. Markowitz SM, Rothkopf M, Holten F, et al: Nafcillin induced agranulocytosis. J Amer Med Assoc 232:1150, 1975
10. Sandberg M, Tuazon CU, Sheagren JN: Neutropenia probably resulting from nafcillin. J Amer Med Assoc 232:1152, 1975
11. Kaneir LM, Tuazon CU, Cardella TE, et al: Comparison of nafcillin and methicillin in the treatment of serious infections due to Staphylococcus aureus. Arch Intern Med (In press)
12. Glew RH, Mollerling RC, Wannerstern C: Comparative synergistic activity of nafcillin, oxacillin, and methicillin in combination with gentamicin against Enterococci. Antimicrob Agents Chemother 7:828, 1975
13. Baldwin DS, Levine BB, McCluskey RT, et al: Renal failure and interstitial nephritis due to penicillin and methicillin. N Engl J Med 279:1245, 1968
14. Bowder WA, Lehman DH, Egan JD, et al: Antitubular basement membrane antibodies in methicillin associated interstitial nephritis. N Engl J Med 291:381, 1974
15. Ids in O, Cuthe T, Willcox RR, et al: Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. Bull WHO 38:159, 1968
16. Weitzman SA, Stossel TP: Drug induced immunological neutropenia. Lancet 1:1068, 1978