ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1980, p. 167-170
0066-4804/80/07-0167/04$02-00/0

Vol. 18, No. 1

# Clinical Trial of Piperacillin with Acquisition of Resistance by *Pseudomonas* and Clinical Relapse

GARY L. SIMON, DAVID R. SNYDMAN, FRANCIS P. TALLY, AND SHERWOOD L. GORBACH*

*Division of Infectious Diseases, Department of Medicine, Tufts-New England Medical Center, Boston, Massachusetts 02111*

A total of 20 serious infections were treated with piperacillin. These infections included bacteremias (5), pneumonias (5), urinary tract infections (5), soft tissue infections (3), septic arthritis (1), and osteomyelitis (1). The most common bacterial pathogen was *Pseudomonas aeruginosa*, accounting for eight infections. The clinical and bacteriological response rates were 75 and 70%, respectively. Four of the five patients who failed to respond to piperacillin therapy were infected with *Pseudomonas*. In two patients with *Pseudomonas* infections clinical relapse was accompanied by the development of piperacillin-resistant *P. aeruginosa*. The findings suggest that the use of piperacillin as a single agent for the treatment of serious gram-negative infections may be ill-advised, especially if *P. aeruginosa* is the offending pathogen.

Gram-negative bacterial infections are a major source of morbidity and mortality among hospitalized patients (13). For several decades the mainstay of treatment for these nosocomial infections has been the aminoglycoside antibiotics. Because these drugs have significant nephrotoxicity and ototoxicity, there has been considerable interest in developing less toxic, alternative agents.

Piperacillin is a new semisynthetic aminobenzylpenicillin with a wide spectrum of activity, including *Escherichia coli, Klebsiella, Enterobacter, Proteus, Serratia, Providencia*, and *Pseudomonas* (1, 4, 7, 12). In vitro, piperacillin is 8- to 16-fold more active than ticarcillin or carbenicillin against *Pseudomonas* and other gram-negative organisms; hence, it was felt that piperacillin alone might be adequate therapy for these infections (1, 7, 12).

A problem which has arisen in the treatment of *Pseudomonas* infections with the semisynthetic penicillins carbenicillin and ticarcillin is the development of resistance to these agents by the offending pathogen (2, 3, 5, 6, 8-11). The results of our therapeutic trial in 20 infections indicate that resistance to piperacillin can also occur during the course of therapy of *Pseudomonas* infection. We report two such instances in our series in whom piperacillin-induced resistance was associated with clinical relapse.

## MATERIALS AND METHODS

All patients were hospitalized at Tufts-New England Medical Center or the Lemuel Shattuck Hospital, Boston, Mass. They were selected for admission to the study by the Infectious Disease staff on the basis of having either documented or presumed serious gram-negative (non-staphylococcal) infection. All patients gave informed written consent before participation. No other antimicrobial agents were administered while patients received piperacillin.

The criterion for bacteremia was positive blood cultures; all bacteremic patients had fever greater than or equal to 38.3°C, hypotension, or rigors or all of these. The diagnosis of pneumonia was based on roentgenological evidence of a pulmonary infiltrate, the presence of polymorphonuclear leukocytes in a smear of the sputum, and a positive culture from sputum. The diagnosis of urinary tract infection was based on fever greater than or equal to 38.3°C, pyuria, and a culture of voided urine which yielded greater than or equal to $10^5$ organisms per ml. The criteria for soft tissue or bone infection included suppuration, erythema, positive cultures, and, in the case of bone infection, roentgenological evidence of osteomyelitis.

Blood for culture was obtained from all patients before therapy. Specimens of urine, sputum, or wound aspirate were obtained when appropriate. Urine specimens were cultured quantitatively and were considered significant when the colony count was greater than or equal to $10^5$/ml of urine. When possible, specimens for culture were obtained during and after therapy.

Piperacillin sodium was reconstituted in 5% glucose and given over 20 min by intravenous infusion every 4 to 6 h. Patients with normal serum creatinines received 250 to 300 g of piperacillin per kg per day. Daily doses varied from 4 g per day in a patient with chronic renal failure to 22 g per day.

Toxicity was monitored by measurements of hemoglobin, hematocrit, differential leukocyte counts, platelets, urinalysis, serum creatinine, and liver function studies, all performed before, during, and after therapy. The patients were examined daily by a member of the Infectious Disease staff.

Efficacy was evaluated when piperacillin was given for at least 72 h. Cure was defined as the absence of systemic or local signs of infection for 48 h, accompanied by eradication of the offending pathogen. Improvement was defined as two of the following: (i)

resolution of fever; (ii) elimination of the pathogen from the site of infection; or (iii) disappearance of local signs of infection. Failure was defined as persistence of systemic or local signs of infection or demise of the patient due to the infectious process. Superinfection was defined as the appearance of a new pathogen accompanied by local or systemic signs of infection.

All initial bacterial isolates were tested for piperacillin susceptibility by the Infectious Disease Research Laboratory at Tufts-New England Medical Center. When appropriate, additional specimens were obtained for culture and susceptibility testing. Piperacillin susceptibility was initially obtained by standardized disk diffusion methods. A zone size of 18 mm or greater indicated that the organism was susceptible to piperacillin. Minimal inhibitory concentrations (MICs) and minimal bactericidal concentrations (MBCs) were determined by broth dilution with microtiter techniques using Mueller-Hinton broth and an inoculum of 0.05 ml of a 6-h broth culture containing $10^5$ colony-forming units per ml.

## RESULTS

A total of 20 infections (in 19 patients) were treated with piperacillin (Table 1). One patient with polycystic kidney disease received piperacillin twice for recurrent *Pseudomonas* urinary tract infections. The patients' ages ranged from 16 to 86 years; 10 were male. The duration of treatment was from 3 to 52 days with a mean of 10 days. The 20 episodes included 5 cases of bacteremic infections, 5 urinary tract infections, 5 pulmonary infections, 3 soft tissue infections, and 1 case each of septic arthritis and chronic osteomyelitis.

Five patients were cured and ten improved with piperacillin therapy, for an overall response rate of 75%. There were five failures including two patients who died as a result of their infection. Two of the five patients who failed had

TABLE 1. *Site of infection, bacteriology, clinical response, and duration of therapy in 20 infectious episodes treated with piperacillin*

| Patient | Site of infection | Bacteriology | Response | Duration of therapy (days) |
|---|---|---|---|---|
| 1 | Bacteremia | *B. vulgatus* | Improved | 10 |
| | Decubitus ulcer | *B. vulgatus, B. ovatus, B. melaninogenicus, P. mirabilis, P. asaccharolyticus, E. coli, Streptococcus* sp. | | |
| 2 | Bacteremia, UTI[b] | *M. morganii* | Improved | 7[a] |
| 3 | Bacteremia | *S. pullorum* | Improved | 11 |
| 4 | Bacteremia, infected hemodialysis graft | *P. aeruginosa* | Failed | 15 |
| 5 | Bacteremia, intraabdominal infection (?) | *P. aeruginosa* | Failed | 15 |
| 6 | Pneumonia | *A. calcoaceticus* | Cured | 6 |
| 7 | Pneumonia | *H. influenzae* | Cured | 10 |
| 8 | Pneumonia | *P. aeruginosa* | Cured | 18 |
| 9 | Pneumonia | *S. pneumoniae* | Improved | 3[c] |
| 10 | Pneumonia | *P. aeruginosa* | Failed | 10 |
| 11 | UTI | *P. aeruginosa* | Cured | 20 |
| 12 | UTI | *P. aeruginosa* | Improved | 5 |
| 13 | UTI | *P. aeruginosa* | Improved | 10 |
| 14 | UTI | *P. vulgaris, E. cloacae*[d] | Improved | 10 |
| 15 | UTI | *K. pneumoniae, P. aeruginosa* | Improved | 3[e] |
| 16 | Decubitus ulcer | *S. aureus, A. calcoaceticus, Proteus* sp. | Improved | 35 |
| 17 | Infected BKA stump[f] | *S. aureus, M. morganii, E. rectali, S. fecalis, B. melaninogenicus* | Cured | 15 |
| 18 | Cellulitis, soft tissue ulcer | *S. rubidia* | Failed | 52 |
| 19 | Chronic osteomyelitis | *K. pneumoniae, E. cloacae, E. aerogenes, S. fecalis* | Improved | 20 |
| 20 | Septic arthritis | *P. aeruginosa* | Failed | 42 |

[a] Developed *S. aureus* superinfection.
[b] UTI, Urinary tract infection.
[c] Left before completion of therapy.
[d] The *E. cloacae* isolate was resistant, and despite clinical improvement, therapy was changed.
[e] Left before completion of therapy.
[f] BKA, Below-the-knee amputation.

bacteremia; the other three failures included a soft tissue infection, a case of pneumonia, and a case of septic arthritis. There was one superinfection.

In 15 of the 20 infections a single pathogen could be incriminated as the causative agent.

These included eight infections with *Pseudomonas aeruginosa*, two with *Acinetobacter calcoaceticus* subsp. *anitratus*, and one each with *Morganella morganii, Haemophilus influenzae, Salmonella pullorum, Serratia rubidia, Enterobacter cloacae*, and *Streptococcus pneumoniae*. More than one microorganism (range, 2 to 7) were isolated from the infected site in five infections, one of which was cured and four of which were improved. Among the five patients who failed to respond clinically, four were infected with *Pseudomonas*, one with a resistant *E. cloacae*, and one with *S. rubidia*.

Three of five bacteremic patients improved with piperacillin. Included in this group were an *M. morganii* urinary tract infection, an infected decubitus ulcer with *Bacteroides vulgatus* bacteremia and an *S. pullorum* infection. The last patient relapsed with recurrent *S. pullorum* bacteremia after 11 days of piperacillin and 2 weeks of oral trimethoprim-sulfamethoxazole therapy. Prolonged intravenous ampicillin and oral amoxicillin therapy was ultimately effective in curing this patient. Both bacteremic patients who failed to respond to piperacillin therapy had *P. aeruginosa* infections, one from an infected hemodialysis graft and the other from an intraabdominal source.

Three of the five patients with pneumonia were cured, and one patient improved with piperacillin. Their infecting organisms were *S. pneumoniae, H. influenzae, P. aeruginosa*, and *A. calcoaceticus* subsp. *anitratus*. The fifth patient died with a *Pseudomonas* pneumonia.

All five urinary tract infections clinically improved with piperacillin therapy. *P. aeruginosa* was the infecting organism in three episodes whereas two pathogens were isolated from each of the other two cases. One patient had *P. aeruginosa* and *Klebsiella pneumoniae*; the other had *Proteus vulgaris* and *E. cloacae*. In the latter patient the *Enterobacter* isolate was resistant to piperacillin and persisted in the urine, but the patient improved clinically with elimination of *Proteus*.

One patient with a polymicrobial soft tissue infection was cured with piperacillin therapy. Two other patients with soft tissue infections (one of whom was bacteremic) improved with piperacillin, as did one patient with chronic osteomyelitis. Two additional patients had progression of their illness despite piperacillin therapy. One patient with *Pseudomonas* arthritis of the knee appeared to respond after 6 weeks of piperacillin therapy. Unfortunately, 6 months later he returned with osteomyelitis of the distal femur due to the same organism. The other patient had an *S. rubidia* cellulitis and soft tissue ulcer on the plantar surface of the foot. Despite 52 days of piperacillin therapy, the ulcer continued to grow *S. rubidia*, although the surrounding cellulitis had resolved. Six weeks after discharge, x-ray changes of osteomyelitis became evident.

In two patients infected with *Pseudomonas*, the organism developed resistance to piperacillin during therapy. In one patient who died with pneumonia the original isolate had an MIC of 1 μg/ml. A second isolate 10 days later had an MIC of 128 μg/ml. The second patient was bacteremic with an infected hemodialysis graft; the initial isolate of *Pseudomonas* had an MIC of 8 μg/ml. This patient defervesced after piperacillin was started, but fever recurred. Repeat blood cultures after 10 days of therapy grew *Pseudomonas* with an MIC of 256 μg/ml. In the latter patient both isolates were identical by pyocin typing.

One patient with an *M. morganii* urinary tract infection and bacteremia developed an *S. aureus* pneumonitis after 7 days of piperacillin therapy, necessitating a change in the antibiotic regimen for this superinfection.

The only symptomatic toxicity noted was the development of ecchymoses in one patient. Interestingly, during a previous hospitalization this patient had developed ecchymoses while receiving carbenicillin. An additional patient had mild, asymptomatic thrombocytopenia during piperacillin therapy.

## DISCUSSION

Piperacillin appears to be an effective agent for the treatment of serious gram-negative infections. The clinical and bacteriological response rates in our patients were 75 and 70%, respectively. This clinical response is slightly, but not significantly, less than the range of 80 to 89% reported by other investigators (O. Cars, T. Linglöt, and F. Nordbring, Program Abstr., Intersci. Conf. Antimicrob. Agents Chemother. [ICAAC] 19th, Boston, Mass., abstr. no. 829, 1979; S. Fuentes del Toro, A. Gomez, M. A. Fuentes del Toro, M. C. Basuald, and E. Echeverria, 19th ICAAC, abstr. no. 828; R. M. Kluge and R. B. Gainer, 19th ICAAC, abstr. no. 831; A. Prince, S. J. Pancoast, and H. C. Neu, 19th ICAAC, abstr. no. 834; J. I. Santos, G. Wenerstrom, B. J. Saxon, and J. M. Matsen, 19th ICAAC, abstr. no. 830).

The excellent in vitro activity of piperacillin against *Pseudomonas* suggested that this antibiotic might be useful in the treatment of patients with infections caused by this pathogen.

Eight patients in this series were infected with *P. aeruginosa*; only four were cured or improved, the other four patients failed to respond to piperacillin. Furthermore, the only deaths in this series occurred in two patients with *Pseu*- with *Pseudomonas* infections.

The use of semisynthetic penicillins in the treatment of *Pseudomonas* infections is accompanied by the development of in vitro resistance and therapeutic failures in a significant number of patients (2, 3, 5, 6, 8–11). Lowbury et al. reported rapid emergence of carbenicillin-resistant *P. aeruginosa* among patients in a burn unit after the introduction of carbenicillin therapy (8). At the Brook Army-Medical Center, Curreri et al. found that 5 of 16 burn patients treated with carbenicillin developed resistant *Pseudomonas* after prolonged therapy for septicemia (2). In a similar vein, Erwin and Bullock noted a 4-fold or greater increase in the MIC for ticarcillin in 7 of 14 patients with *Pseudomonas* infections (5). Prince et al. recently reported the development of piperacillin resistance in 3 of 32 cases, but all isolates were successfully eradicated from the infected site (A. Prince, S. J. Pancoast, and H. C. Neu, 19th ICAAC, abstr. no. 834, 1979). In our study *Pseudomonas* strains from two of eight infected patients developed resistance during piperacillin therapy. In both cases, the development of resistance was associated with clinical relapse. To our knowledge, this is the first reported instance of piperacillin failure accompanied by the development of resistance in *Pseudomonas*.

Clinical efficacy of an antibiotic is dependent not only on its antimicrobial activity but also on host defense mechanisms. In a noncomparative trial such as this, it is often difficult to evaluate the relative roles of host defenses and antibiotic failure. Nevertheless, the significant progression of disease which occurred in five patients with susceptible organisms and the development of resistance by two of eight *Pseudomonas* isolates suggest that it may be ill advised to use piperacillin alone in the therapy of serious gram-negative infections, especially when *P. aeruginosa* is the offending pathogen.

## LITERATURE CITED


1. **Bodey, G. P., and B. LeBlanc.** 1978. Piperacillin: in vitro evaluation. Antimicrob. Agents Chemother. **14**:78–87.
2. **Curreri, P. W., R. B. Lindberg, F. C. DiVincenti, and B. A. Pruitt, Jr.** 1970. Intravenous administration of carbenicillin for septicemia due to *Pseudomonas aeruginosa* following thermal injury. J. Infect. Dis. **122**: S40–S47.
3. **Darrell, J. H., and P. M. Waterworth.** 1969. Carbenicillin resistance in *Pseudomonas aeruginosa* from clinical material. Br. Med. J. **3**:141–143.
4. **Dickinson, G. M., T. J. Cleary, and T. A. Hoffman.** 1978. Comparative evaluation of piperacillin in vitro. Antimicrob. Agents Chemother. **14**:919–921.
5. **Ervin, F. R., and W. E. Bullock.** 1976. Clinical and pharmacological studies of ticarcillin in gram-negative infections. Antimicrob. Agents Chemother. **9**:94–101.
6. **Hoffman, T. A., and W. E. Bullock.** 1970. Carbenicillin therapy of *Pseudomonas* and other gram-negative bacillary infections. Ann. Intern. Med. **73**:165–171.
7. **Jones, R. N., C. Thornsberry, A. L. Barry, P. C. Fuchs, T. L. Gavan, and E. H. Gerlach.** 1977. Piperacillin (T-1220), a new semisynthetic penicillin: in vitro antimicrobial activity comparison with carbenicillin, ticarcillin, ampicillin, cephalothin, cefamandole, and cefoxitin. J. Antibiot. **30**:1107–1114.
8. **Lowbury, E. J. L., H. A. Lilly, A. Kidson, G. A. J. Ayliffe, and R. J. Jones.** 1969. Sensitivity of *Pseudomonas aeruginosa* to antibiotics: emergence of strains highly resistant to carbenicillin. Lancet **ii**:448–452.
9. **Lyons, R. W., G. F. Thornton, and V. T. Andriole.** 1970. Carbenicillin: clinical and laboratory studies. J. Infect. Dis. **122**:S104–S114.
10. **Marks, M. I., and T. C. Eickhoff.** 1970. Carbenicillin: a clinical and laboratory evaluation. Ann. Intern. Med. **73**:179–187.
11. **Smith, C. B., J. N. Wilfert, P. E. Dans, T. A. Kurrus, and M. Finland.** 1970. In-vitro activity of carbenicillin and results of treatment of infections due to *Pseudomonas* with carbenicillin singly and in combination with gentamicin. J. Infect. Dis. **122**:S14–S28.
12. **Wise, R., J. M. Andrews, and K. A. Bedford.** 1978. Comparison of the in vitro activity of Bay k 4999 and piperacillin, two new antipseudomonal broad-spectrum penicillins, with other β-lactam drugs. Antimicrob. Agents Chemother. **14**:549–552.
13. **Wolff, S. M., and J. V. Bennett.** 1974. Gram-negative rod bacteremia. N. Engl. J. Med. **291**:733–734.