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Prospective Randomized Trial of Piperacillin Monotherapy Versus Carboxypenicillin-Aminoglycoside Combination Regimens in the Empirical Treatment of Serious Bacterial Infections

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Piperacillin as a single agent was compared in a prospective randomized trial with carboxypenicillin-aminoglycoside combinations in empirical therapy of serious bacterial infections. The difference in the clinical response rates with piperacillin (77% of 26 infection episodes) and combination therapy (75% of 24 infection episodes) were not statistically significant. Fewer adverse effects occurred in the piperacillin-treated group (42%) than in the combination-treated group (71%) ($P = 0.0399$ by Fisher's exact test), although neither nephrotoxicity nor hypokalemia alone was significantly less frequent in patients receiving piperacillin. However, the emergence of resistant organisms during therapy was more frequent among patients receiving piperacillin alone (42% of patients) than among patients receiving combination therapy (17% of patients) ($P = 0.0465$ by Fisher's exact test). Moreover, emergence of resistance accounted for 5 of 9 patients with treatment failure, superinfection, or both when piperacillin was used as a single agent, compared with 2 of 10 similar patients in the combination group ($P = 0.1299$ by Fisher's exact test). The use of piperacillin as a single agent in the treatment of serious bacterial infections is not advocated, and the addition of an aminoglycoside to prevent emergence of resistance during empirical therapy of such infections is strongly recommended.

Carboxypenicillins (such as carbenicillin or ticarcillin) are frequently used in combination with an aminoglycoside in the initial treatment of serious infections. Such a combination offers the potential advantages of an enhanced antibacterial spectrum, possible synergistic activity, and deterrence of bacterial resistance during therapy (21). However, despite numerous clinical trials, the superiority of combination therapy over monotherapy has not been convincingly demonstrated (21). The advent of a new piperazine-penicillin, piperacillin, which has remarkable broad-spectrum activity and minimal toxicity, has made the prospect of monotherapy for serious infections particularly attractive. Piperacillin has superior in vitro activity against *Pseudomonas*, *Klebsiella*, *Enterobacter*, indole-positive *Proteus*, *Enterococcus*, and *Bacteroides* species compared with carbenicillin and ticarcillin (2, 7, 13). It was found to be effective as monotherapy for a variety of bacterial infections in early clinical trials (20). It does not have the nephrotoxic or ototoxic potential of aminoglycosides. Since piperacillin is a monosodium salt (sodium content, 1.98 meq/g), compared with the disodium salts carbenicillin (4.7 meq/g) and ticarcillin (5.2 meq/g), and is used at a lower equivalent therapeutic dose, it may be expected to cause less hypokalemia. For these reasons, we examined in a prospective and randomized study design the efficacy and adverse effects of piperacillin monotherapy as compared with carboxypenicillin-aminoglycoside combination regimens in empirical treatment of serious bacterial infections.

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MATERIALS AND METHODS

Patients. Adult patients from Vancouver General Hospital (1979-81) with clinical signs and symptoms of serious infection known or suspected to be due to organisms susceptible to the study drugs were eligible for enrollment. The following infections were included: urinary tract infections (excluding asymptomatic bacteriuria and cystitis), respiratory tract infections, skin and soft tissue infections, osteomyelitis, intraabdominal infections, and suspected septicemia in febrile

granulocytopenic cancer patients (granulocyte count below 1,000/μl, temperature greater than 38.3°C on at least two separate occasions). Patients were excluded if the infecting organism was known to be resistant to the study drugs or if they were already receiving potentially effective antimicrobial therapy. Also excluded were patients with moderate renal insufficiency (serum creatinine > 3 mg/dl), pregnant or nursing women, and patients with hypersensitivity to any of the study drugs. Informed written consent was obtained from each patient (or relative) in accordance with the guidelines of the University of British Columbia Human Experimentation Committee.

Study drugs. Eligible patients were assigned to either piperacillin monotherapy or combination regimens, using a computer-generated randomization schedule. Piperacillin (150 mg/kg per day for urinary tract infections, 300 mg/kg per day for all others; maximum dose, 18 g/day) was administered intravenously at 4-h intervals. The combination regimen consisted of carbenicillin (250 mg/kg per day for urinary tract infections, 500 mg/kg per day for all others; maximum dose, 30 g/day; administered every 4 h intravenously) plus gentamicin (4.5 mg/kg per day, administered every 8 h intravenously). The dose of gentamicin was adjusted during therapy to maintain peak serum gentamicin levels of 5 to 10 μg/ml and trough serum gentamicin levels of <2 μg/ml. At the discretion of the investigator, ticarcillin was substituted for carbenicillin or tobramycin was substituted for gentamicin, or both substitutions were made. Antistaphylococcal therapy with cloxacillin was added for either group if clinically indicated. In febrile granulocytopenic patients, trimethoprim-sulfamethoxazole prophylaxis was continued at the discretion of the attending physician in either group.

Treatment was continued until the patient had been afebrile for at least 3 days, unless clinical failure occurred or other specific therapy was deemed necessary.

Laboratory studies. Patients were examined daily during treatment and were followed for 2 weeks thereafter or until they were discharged from the hospital. Cultures of blood and urine, in addition to appropriate cultures from the suspected site of infection, and laboratory measures of renal, hemopoietic, and hepatic function were performed before treatment, every 4 days during treatment, and at 24 to 72 h after completion of treatment. In the case of urinary tract infections, additional urine cultures were obtained at 5 to 9 days and 4 to 6 weeks posttreatment. Serum gentamicin or tobramycin levels were determined at least weekly and as often as clinically indicated by radioimmunoassay (14). Causative organisms were identified by standard criteria (3, 5, 6, 8–10, 16, 17). Antimicrobial susceptibility of facultative isolates was determined by the Kirby-Bauer disk diffusion method according to established criteria for each of the study drugs (1, 11). Antimicrobial susceptibility of obligate anaerobes against carbenicillin, ticarcillin, or piperacillin was determined by either the disk-broth method (19) or the agar-dilution technique (4).

Evaluation. Each febrile episode, based on clinical findings and microbiological data, was classified as (i) bacteriologically documented infection—definite signs and symptoms revealing a site of infection, confirmed by culture; (ii) clinically documented infection—signs and symptoms of infection with an identifiable site but without bacteriological proof of the causative organism; or (iii) clinically suspected infection—fever without an identifiable site of infection or bacteriological proof of infection. The latter episodes usually occurred in granulocytopenic cancer patients.

Clinical responses were classifed as (i) cure—no evidence of infection at the end of treatment or during the follow-up period; (ii) improvement—significant but incomplete resolution of infection; or (iii) failure—no response to treatment, or relapse during treatment or the follow-up period.

Bacteriological responses were judged as (i) elimination—eradication of the infecting pathogen in follow-up cultures; (ii) persistence—the infecting pathogen remained; or (iii) indeterminate—bacteriological response was inevaluable (e.g., no pathogen isolated or follow-up cultures not obtained).

Superinfection was defined as the presence of signs and symptoms of infection due to a new organism occurring either at the initial or a different infection site during antimicrobial therapy. Colonization was defined as the acquisition of a new organism isolated from the infection site during or after therapy but without fever and other clinical signs of infection.

Antibiotic-related hypokalemia was defined as a fall in the serum potassium level by >1.0 meq/dl from pretreatment values to ≤3.5 meq/dl during therapy in the absence of other potassium-depleting factors such as diarrhea or diuretic or amphotericin B therapy. Antibiotic-related nephrotoxicity was defined as an increase in the serum creatinine level by >0.5 mg/dl from pretreatment values when other possible causes of nephrotoxicity (e.g., hypotension, other nephrotoxic drugs, etc.) had been excluded.

RESULTS

Study patients. Forty-two patients with 54 separate episodes of infection were enrolled in the study. Four episodes were excluded from analysis: one cancer patient with fever and granulocytopenia subsequently proved to have a candida urinary tract infection, and three others died within 72 h of treatment of causes unrelated to bacterial infection (disseminated candidiasis, myocardial infarction, and malignancy, respectively). Of the remaining 50 infection episodes, 26 were treated with piperacillin and 24 were treated with combination therapy. The demographic characteristics, underlying disease, sites of infection and causative organisms, and concomitant therapy were comparable in the two groups (Tables 1 and 2). The patients selected for study were seriously ill; more than half had rapidly or ultimately fatal underlying disease (McCabe-Jackson classification) (12). *Pseudomonas aeruginosa* was the most common causative organism and was isolated in 11 (42%) piperacillin-treated episodes and 8 (33%) combination-treated episodes. Infection was polymicrobial in 12 (46%) piperacillin-treated episodes and 9 (35%) combination-treated episodes. Aerobic gram-positive cocci (including enterococci)

TABLE 1. Patient characteristics

Characteristic	No. in following treatment group:	
	Piperacillin	Combination
Infection episodes	26	24
Bacteriologically documented	21	17
Clinically documented	1	4
Clinically suspected	4	3
Mean age in years (range)	49 (16–75)	46 (16–80)
Sex (male/female)	17/9	13/11
Underlying disease[a]		
Rapidly fatal	12	18
Ultimately fatal	4	2
Nonfatal	10	4
Granulocytopenia (<1,000/μl)	12	18
Granulocyte (<100/μl)	11	13
Failed previous therapy	8	4
Study regimens		
Piperacillin	26	
Carbenicillin-gentamicin		17
Carbenicillin-tobramycin		4
Ticarcillin-gentamicin		2
Ticarcillin-tobramycin		1
Concomitant therapy	18	15
Cloxacillin	10	7
Trimethoprim-sulfamethoxazole[b]	6	7
Amphotericin B	3	0
Acyclovir	0	1

[a] McCabe-Jackson classification (12).
[b] As chemoprophylaxis in patients with granulocytopenia.

were present in most of these polymicrobial infections.

Bacteremia was documented in two piperacillin-treated and five combination-treated infection episodes before initiation of therapy (Table 2). One of these patients in the combination-treated group had *Staphylococcus epidermidis* bacteremia associated with an infected venous catheter. She initially responded both clinically and bacteriologically, but later developed a polymicrobial bacteremia (*P. aeruginosa*, *S. epidermidis*, and viridans streptococci) when treatment was prematurely discontinued on day 6 because of a suspected toxic reaction to the study drugs. This was considered both a treatment failure and a superinfection. In three other patients with combination therapy, bacteremia developed either during therapy (two patients) or within 24 h after completion of therapy (one patient). These were considered "breakthrough bacteremias" with the original causative organisms (*Escherichia coli*, *Klebsiella pneumoniae*, and *Bacteroides melaninogenicus*, respectively).

Response to therapy. Clinical response with cure or improvement occurred in 20 (77%) episodes in the piperacillin-treated group and 18 (75%) episodes in the combination-treated group (Table 3). Clinical failure occurred in six episodes in each group (23% and 25%, respectively). Death due to infection occurred in two patients treated with piperacillin and three patients treated with combination therapy. Among the patients with granulocytopenia at enrollment, clinical cure or improvement occurred in 10 of 12 (83%) piperacillin-treated and 15 of 18 (83%) combination-treated patients. Superinfection developed in five patients treated with piperacillin and four patients treated with combination antibiotics. *S. epidermidis* complicating intravenous lines and urinary tract infection from enterococci, klebsiellae, enterobacters, or candidae were the most frequent superinfections encountered.

TABLE 2. Infection sites and pathogens[a]

Infection	No. (no. with bacteremia) in following treatment group:	
	Piperacillin (n = 26)	Combination (n = 24)
Site		
Skin or soft tissue	7 (1)	13 (2)
Pneumonia	4	4 (1)[b]
Upper respiratory tract	5 (1)	1 (1)
Urinary tract	6	1 (1)[b]
Intraabdominal	1	3 (1)[b]
Bone	3	1
Venous catheter	0	1 (1)
Source unknown	4	4 (1)
Pathogens isolated		
Pseudomonas	11	8 (1)
Klebsiellae	3	1 (1)[b]
E. coli	4 (1)	5 (2)[b]
Other aerobic gram-negative bacilli	10	2
S. aureus	4	4
S. epidermidis	1	5 (1)
Streptococci	3 (1)	6 (1)
Enterococci	6	1
Bacteroides	2	4 (1)[b]
Peptococcaceae	3	3
Anaerobic gram-positive bacilli	3	1 (1)
Other	2	1
Polymicrobial	12	9

[a] Multiple sites and pathogens in some cases.
[b] Bacteremia occurred during or after discontinuation of therapy in one case each (see text).

Among patients with bacteriologically documented infection, the causative pathogen was eliminated in 52% of the piperacillin-treated group and 59% of the combination-treated group (Table 3). Bacteriological failure with persistence of the causative pathogen occurred in eight and five episodes, respectively. *P. aeruginosa* accounted for five of eight bacteriological failures in the piperacillin-treated group and one of five in the combination-treated group ($P = 0.1795$ by Fisher's exact test).

Emergence of resistance. Resistant isolates occurred more frequently during piperacillin therapy (11 of 26; 42%) than during combination therapy (4 of 24; 17%) ($P = 0.0465$ by Fisher's exact test) (Table 4). Emergence of resistant organisms was associated with clinical treatment failure in three cases with piperacillin and none with combination therapy and was associated with superinfection in four cases treated with piperacillin and two cases receiving combination therapy.

TABLE 3. Clinical and bacteriological response to treatment

Response	No. (%) in following treatment group:	
	Piperacillin ($n = 26$)	Combination ($n = 24$)
Clinical		
Cure or improvement	20 (77)	18 (75)
Treatment failure	6 (23)	6 (25)
Pneumonia	3	1
Urinary tract infection	1	1
Osteomyelitis	2	0
Pancreatic abscess	0	1
Invasive burn wound	0	1
Febrile granulocytopenia	0	2
Superinfection	5 (19)	4 (17)
Urinary tract	2	1
Intravenous line	1	3
Skin and soft tissue	2	0
Treatment failure, superinfection, or both	9 (35)	10 (42)
Bacteriological		
Documented infection	21	17
Pathogen eliminated	11 (52)	10 (59)
Bacteriologic persistence	8	5
Pseudomonas	5	1
Klebsiellae	2	1[a]
E. coli	1	1[a]
Enterobacters	1	0
Citrobacters	1	0
Bacteroides	0	1[a]
Enterococci	2	1
S. aureus	2	1
S. epidermidis	0	1[b]
Clostridium perfringens	1	0
Indeterminate[c]	2	2

[a] With breakthrough bacteremia.
[b] With bacteremia.
[c] No posttreatment cultures.

Adverse effects. Hypokalemia during antibiotic therapy developed in 7 (27%) patients treated with piperacillin and 10 (42%) patients receiving combination therapy. Serum creatinine rose by 0.5 mg/dl in two (7.6%) patients treated with piperacillin (including one patient with probable interstitial nephritis) and in five (25%) patients receiving combination therapy. These differences were not statistically significant. Other adverse effects included diarrhea (two patients in each treatment group), eosinophilia and skin rash (two and one patients, respectively, in the piperacillin group), and hemolysis and hepatitis (one patient each in the combination group). Overall, 11 of 26 (42%) patients receiving piperacillin and 17 of 24 (71%) patients receiving combination therapy were associated with development of one or more adverse effects ($P = 0.0399$ by Fisher's exact test).

DISCUSSION

In this study involving a relatively small number of patients, no significant difference in clinical response was demonstrated between piperacillin as monotherapy and combination regimens with carbenicillin or ticarcillin plus an aminoglycoside in the empirical therapy of serious bacterial infections. This should not be taken to mean that piperacillin as a single agent is as effective as combination therapy, since the sample size was small, and, although the differences were not statistically significant, fewer patients treated with piperacillin had rapidly fatal underlying disease, granulocytopenia, or bacteremia. Futhermore, 10 of the 26 patients given piperacillin also received cloxacillin and thus were not treated with piperacillin alone. More alarming is the finding of increased isolation of resistant organisms during piperacillin monotherapy (42 versus 17% of patients; $P < 0.05$). Moreover, emergence of resistant organisms accounted for five of the nine patients with treatment failure, superinfection, or both when piperacillin was used as a single agent, compared with two of ten similar patients in the combination group. Pseudomonas as well as other aerobic gram-negative bacilli and enterococci were the major isolates acquiring resistance during piperacillin monotherapy in our study, similar to the experience of Winston et al. (20) and Simon et al. (15). In contrast, Wade et al. (18) found that only 8% of

TABLE 4. Emergence of resistance during therapy

Resistance	No. (%) in following treatment group:		P[a]
	Piperacillin (n = 26)	Combination (n = 24)	
Emergence of resistant isolates during therapy	11 (42)	4 (17)	0.0465
Original organism	6	2	
New organism	8	2	
Treatment failure, superinfection, or both due to emergence of resistance	5 (19)	2 (8)	0.2437
Proportion of all patients with treatment failure, superinfection, or both due to resistance	5/9	2/10	0.1299
Treatment failure	3/6	0/6	
Superinfection	4/5	2/4	
Resistant isolates			
Enterococci	3	0	
S. aureus	1	0	
S. epidermidis	2	3	
E. coli	3	0	
Klebsiellae	3	0	
Pseudomonas	3	0	
Citrobacters	1	0	
Serratiae	1	0	
Enterobacters	1	0	
Candidae	1	1	

[a] By Fisher's exact test.

patients acquired piperacillin-resistant organisms during piperacillin-amikacin combination therapy.

Another potential disadvantage of the use of piperacillin as a single agent for empirical therapy is its relatively poor activity against *Staphylococcus aureus* and *S. epidermidis* (2, 7). In our prospective study, addition of anti-staphylococcal therapy was considered clinically indicated in 10 of 26 (38%) patients receiving piperacillin and in 7 of 24 (29%) patients receiving combination therapy. Either *S. aureus* or *S. epidermidis* was isolated as a significant pathogen in 14 of 38 (37%) patients with bacteriologically documented infection in this series.

We did not find a significantly lower incidence or less severity of either hypokalemia, bleeding diathesis due to platelet dysfunction, or antibiotic-associated nephrotoxicity in patients treated with piperacillin. However, patients treated with piperacillin alone experienced fewer adverse effects overall compared with patients receiving combination therapy ($P < 0.05$). The rather high overall incidence (71%) of adverse effects in the combination-treated group was attributed to the frequent occurrence of hypokalemia when carbenicillin was included in the regimen.

Despite its excellent in vitro activity and demonstrated efficacy, use of piperacillin as a single agent in the treatment of serious bacterial infections is not advocated. Addition of an aminoglycoside to prevent emergence of resistance during empirical therapy of such infections is strongly recommended.

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