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Efficacy, safety and tolerance of parenteral piperacillin/tazobactam in the treatment of patients with lower respiratory tract infections

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An open, non-comparative multicentre study was conducted at 36 sites in six countries to test the efficacy and safety of piperacillin/tazobactam in the therapy of lower respiratory tract infections. Piperacillin 4 g and tazobactam 500 mg were administered intravenously every 8 h for a minimum of five days. Two hundred and thirty patients were enrolled: 133 were evaluable for clinical efficacy and 106 for bacteriological efficacy. The clinical response was favourable in 96% of evaluable patients and the bacterial eradication rate was 93%. Nine patients (4%) had severe adverse events related to piperacillin/tazobactam and requiring discontinuation of therapy. In this study piperacillin/tazobactam was an effective and safe drug in the treatment of hospitalized patients with lower respiratory tract infection caused by sensitive organisms.

Introduction

Piperacillin sodium is a broad-spectrum semisynthetic penicillin administered parenterally. It has been widely used in the treatment of serious lower respiratory tract infections (Winston *et al.*, 1980; Gooding, Clark & Sathe, 1982; Mouton, Beuscart & Soussy, 1986). However, the spread of β-lactamase producing organisms is a problem (Philippon, Paul & Nevot, 1987), especially among strains of *Staphylococcus* spp., *Haemophilus influenzae, Moraxella catarrhalis, Escherichia coli* and *Klebsiella* spp.

In-vitro studies have shown that the β-lactamase inhibitor tazobactam restores the activity of piperacillin against β-lactamase producing staphylococci and a wide variety of resistant Gram-negative bacteria (Kuck *et al.*, 1989; Weiss *et al.*, 1989).

Since most pathogens isolated from lower respiratory tract infections can be expected to fall within the extended spectrum of activity of piperacillin/tazobactam, a prospective study was performed to test the efficacy and safety of this combination in the therapy of lower respiratory tract infections.

Patients and methods

From November 1988 to January 1990, an open non-comparative, multi-centre study was conducted in 36 hospitals, in six countries. This study was approved by appro-

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priate Ethics Committees and was conducted in accordance with the Declaration of Helsinski. Informed consent was obtained before enrolment of the patient.

Patient selection

Hospitalized patients with a minimum age of 18 years, suffering from a clinically or bacteriologically confirmed lower respiratory tract infection, caused by bacteria, thought to be susceptible to piperacillin/tazobactam, were eligible for entry into the study.

Clinical criteria for enrolment included the recent onset or increase in purulent sputum, a temperature of $> 38°C$ and/or a peripheral white blood cell count of $> 10{,}000/m^3$. Chest X-rays were required to classify a case of pneumonia as opposed to bronchitis. Female patients with child-bearing potential were enrolled if they had a negative pregnancy test within 24 h before enrolment and if they practised sexual abstinence or used a medically accepted form of birth control during the treatment period.

Patients were excluded in cases of: known allergy to β-lactam antibiotics or β-lactamase inhibitors; too severe lower respiratory tract infection (septic shock, use of mechanical ventilation with either a positive end-expiratory pressure > 5 cm H_2O or an $FiO_2 > 60\%$); concomitant use of probenecid or antibiotics; use of another antibacterial agent within the past 72 h (unless this had proved to be clinically and bacteriologically ineffective); presence of a pathogen known to be resistant to piperacillin/tazobactam; presence of *Pseudomonas aeruginosa*; administration of any investigational drug within one month before enrolment; severe renal impairment (serum creatinine > 225 mmol/L) serious hepatic disease (serum transaminases, alkaline phosphatase or bilirubin more than twice the normal upper limit); haematological disturbances (leukaemia, granulocyte count $< 1000/mm^3$ or platelet counts $< 50{,}000/mm^3$). The patients with the following conditions were also excluded: cystic fibrosis; bronchial obstruction; lung abscess; empyema; lung cancer or metastastic lung disease; artificial heart valve or vascular prosthesis; tuberculosis or any other concomitant infection (except intra-abdominal infection); and AIDS or HIV antibody positivity.

Administration of drug

Piperacillin 4 g and tazobactam 500 mg were administered every 8 h by intravenous infusion over 30 min. Each patient was to be treated for a minimum of five days although it was recommended that in patients who exhibited a satisfactory clinical response, treatment should be continued for at least two days after the resolution of signs and symptoms.

Study procedures

A complete medical history, physical examination and chest X-ray of the patient was performed before entry into the study. Evaluations to determine response to therapy were made daily for the first week of therapy; every two to three days thereafter during treatment; on the last day of therapy (end-point); one to three days (early follow-up) and ten to 14 days (late follow-up) after completion of therapy. A repeat chest x-ray was required only in patients with persisting clinical signs of active infections or in those who were withdrawn because of treatment failure or adverse reaction.

Before the start of treatment cultures of blood and respiratory secretions were obtained to document the presence of pathogens. Additional cultures were taken after three to four days of therapy; one to three days and ten to 14 days post-treatment; and on the last day of treatment for patients withdrawn early from the study. Microorganisms were isolated and identified according to standard bacteriological methods. The degree of susceptibility to piperacillin/tazobactam was recorded for each pathogen.

The safety of piperacillin/tazobactam was judged by the following laboratory parameters: complete blood cell and differential leucocyte and platelet count; prothrombin time; direct Coombs' test; serum electrolytes, urea, creatinine, total bilirubin, alkaline phosphatase, transaminases (SGOT, SGPT), blood glucose, albumin, total protein and uric acid; and urinalysis and microscopy of the sediment. Laboratory evaluations were performed before treatment, every three to five days during treatment, one to three days and ten to 14 days post-treatment and on the last day of therapy if a patient was withdrawn early from the study.

Adverse clinical experiences during treatment were recorded and the relationship of the event to the study therapy assessed by the treating clinician.

Evaluation of therapy

To be considered for clinical efficacy, a patient must have met all the inclusion and exclusion criteria and should have had (a) treatment with piperacillin/tazobactam for at least five days and (b) at least one end-of-therapy or post-therapy clinical evaluation.

Clinical response was classified as follows: (a) cure: the patient was asymptomatic with no evidence of active infection at the time treatment was completed and at the post-therapy evaluation; (b) improvement: significant improvement of symptoms on evaluation but with persisting evidence of infection (c) relapse: clinical improvement followed by deterioration during therapy or at the post-treatment evaluation (d) failure: no significant response to therapy or inability to tolerate the study drug.

For bacteriological evaluation, a patient must have met the clinical evaluability criteria as well as having had the following: (a) presence of pre-therapy pathogen(s) susceptible to piperacillin/tazobactam; (b) availability of susceptibility data; (c) at least one end-of-therapy or post-therapy bacteriological evaluation. Bacteriological response was graded as follows: (a) eradication: the original pathogen(s) eradicated in culture taken during or after treatment (or presumptively eradicated based upon clinical response); (b) persistence: presence of the original pathogen(s) in culture taken during or after treatment; (c) superinfection (early follow-up) or reinfection (late follow-up): all baseline pathogens eradicated, but one or more new pathogens present in culture taken at early or late follow-up respectively.

Results

A total of 230 patients was enrolled. Of these, 133 (58%) were considered evaluable for clinical efficacy and 106 (46%) for bacteriological efficacy.

The primary reasons for non-evaluability are summarized in Table I. The predominant reason for exclusion from clinical evaluation was inadequate regimen ($n = 20$); 32 patients were excluded from bacteriological evaluation because no pathogen was isolated.

Table I. Primary reasons for clinical and bacteriological non-evaluability

Reason for exclusion	Number of patients who were not evaluable Clinically	Bacteriologically
Abnormal laboratory values before therapy	15	12
Resistant pathogen(s) before therapy	8	8
Pre-study antimicrobial therapy	15	12
Inadequate signs and symptoms	14	14
Concomitant antimicrobial therapy	8	7
Inadequate regimen	20	14
Missed visits	7	10
No pathogen(s) isolated	—	32
No susceptibility test	—	8
Other	10	7
Total	97	124

Characteristics of patients

The ages and sexes of patients in the whole group ($n = 230$), the clinically evaluable group ($n = 133$) and the bacteriologically evaluable group ($n = 106$), were very similar. The commonest diagnosis was pneumonia followed by bronchitis and bronchopneumonia (Table II). Most infections were community-acquired, with a level of 52% (120/230) overall. This increased to 63% in the clinically evaluable group (84/133) and in the bacteriologically evaluable group (67/106). The mean duration of infections was 6·0 days for all patients, 4·5 days for clinically evaluable patients and 4·9 days for bacteriologically evaluable patients.

Twenty-seven patients were treated with other antibacterial agents during the 72 h immediately preceding the initiation of the study medication; 22 of these patients were excluded from analysis. Of the remaining five patients, one received acceptable prophylaxis only and four had documented resistance to the antibacterial agents used.

Table II. Characteristics of patients

Characteristics	Total ($n = 230$)	Clinically evaluable patients ($n = 133$)	Bacteriologically evaluable patients ($n = 106$)
Mean age (years)	57·5 (S.D. 17·3)	55·6 (S.D. 18·0)	55·2 (S.D. 17·9)
Range (years)	18–90	18–90	18–87
Sex			
male	157	87	66
female	73	46	40
Diagnosis			
Pneumonia	161	90	70
Bronchitis	36	25	21
Bronchopneumonia	21	11	9
Acute LRTI[a]	10	5	5
Pneumonia with pleurisy	2	2	1

[a] LRTI, Lower respiratory tract infection; site of infection not determined.

Table III. Pathogens isolated before therapy in bacteriologically evaluable patients

Organism	Number of isolates
S. aureus	15
Coagulase-negative staphylococci	5
S. pneumoniae	24
Other streptococci	13
Acinetobacter spp.	6
Aeromonas spp.	1
Citrobacter spp.	3
Enterobacter spp.	7
E. coli	9
Haemophilus spp.	19
Klebsiella spp.	21
M. catarrhalis	2
Proteus spp.	7
Serratia spp.	2
Other Gram-negative bacilli[a]	1
Neisseria spp.	4
Corynebacterium spp.	1
Bacteroides spp.	2

[a]Gram stain identification without subculture.

Bacteriological results

A total of 142 pathogens was isolated before treatment from the 106 bacteriologically evaluable patients (Table III). In most patients only one pathogen was isolated (80/106). Eighteen patients had two pathogens, six patients had three and two patients had four.

The most prevalent organisms were *Streptococcus pneumoniae* with 24 out of the 142 isolates (17%), *Klebsiella pneumoniae* with 18 isolates (13%) and *H. influenzae* with 17 isolates (12%).

Among the 142 pathogens, 15 were piperacillin-resistant, but susceptible to piperacillin/tazobactam. These were isolated from 14 bacteriologically evaluable patients. The commonest pathogen of this type was *Staphylococcus aureus* ($n = 7$), followed by coagulase-negative staphylococci ($n = 4$), *K. pneumoniae* ($n = 1$), *Klebsiella oxytoca* ($n = 1$), *Proteus morganii* ($n = 1$) and *Neisseria* sp. ($n = 1$).

Clinical efficacy

The clinical response of the 133 clinically evaluable patients on the last day of therapy, and at the early and late follow-up evaluations are shown in Table IV.

At the early follow-up, 131 of the 133 evaluable patients had an interpretable response. Of these, 127 were clinically cured (111 of 131; 85%) or improved (16 of 131; 12%), while 4 patients (3%) failed therapy. Patients with bronchopneumonia, undefined lower respiratory tract infection (site of infection not determined) or pneumonia with pleurisy were all cured; 86 of 88 patients with pneumonia were also cured or improved. In the 25 patients with bronchitis, two (8%) failed therapy.

Table IV. Clinical response among evaluable patients

Outcome	Last day of therapy	Early follow-up	Late follow-up
Cure	114	111	72
Improvement	13	16	1
Relapse	2	—	2
Failure	4	4	—
Total	133	131	75

A total of 75 patients returned for a late assessment. Of these 73 were assessed as cured or improved while two relapsed: one case of bronchitis was classified as relapsed because of persistence of the original pathogen; the other had a relapse of pneumonia due to a reinfection.

Bacteriological response

Of 106 bacteriologically evaluable patients, 104 attended for early follow-up. The pathogen was presumptively eradicated in 47 patients. Among the remainder, eradication was documented in 50, the original pathogen persisted in 4 and there were three superinfections (Table V).

The four isolates which persisted at early follow-up were *Streptococcus pyogenes*, *S. aureus* and two *Acinetobacter* spp.

At the late follow-up, 66 patients returned for assessment. Of these, 60 (91%) had a favourable response (presumed or documented eradication) while two patients (3%) showed evidence of persistence and four patients (6%) had a reinfection. The two persisting organisms were *S. aureus* and *S. pneumoniae*. The latter organism had been presumed eradicated at early follow-up.

Among the 15 patients with pathogens that were piperacillin-resistant but susceptible to piperacillin/tazobactam, 14 were evaluable for early follow-up. All pathogens were eradicated; of 11 patients attending late follow-up, only one showed persistence (*S. aureus*).

The bacteriological responses of all patients attending early and late follow-up are summarized for each diagnostic category in Table VI.

Table V. Bacteriological response among bacteriologically evaluable patients

Outcome	Early follow-up	Late follow-up
Documented eradication	50	25
Presumptive eradication	47	35
Persistence	4	2
Superinfection	3	—
Re-infection	—	4
No follow up	2	40
Total	106	106

Table VI. Bacteriological responses in patients attending early and late follow-up by the primary diagnosis

Diagnosis	Early follow-up				Late follow-up			
	total	eradication	persistence	superinfection	total	eradication	persistence	reinfection
Pneumonia	68	65	2	1	52	49	1	2
Bronchitis	21	20	1	0	8	7	1	0
Bronchopneumonia	9	8	0	1	4	3	0	1
Pneumonia with pleurisy	1	1	0	0	0	0	0	0
Undefined lower respiratory tract infection[a]	5	3	1	1	2	1	0	1
Total	104	97	4	3	66	60	2	4

[a]Site of infection not determined.

Duration of therapy

The mean duration of treatment was 9·1 days for all patients, 9·6 days for clinically evaluable patients and 10·0 days for bacteriologically evaluable patients.

Mortality

Sixteen patients died during or within 30 days of treatment with piperacillin/tazobactam. In only one patient was death thought to be possibly drug related: he died on the third day of therapy from acute infection and lack of efficacy of the study drug.

Adverse reactions

Thirty-six of the 230 patients enrolled reported a total of 54 adverse events. The commonest side-effects were diarrhoea (17), stool changes (3), vomiting (2), erythema (3), exanthema (1), rash (2) and urticaria (1). In nine patients, a total of 17 adverse experiences necessitated permanent discontinuation of therapy.

Eighty laboratory test abnormalities definitely, possibly or probably related to study therapy were reported. Twenty were classified as haematological (platelet or eosinophil counts outside the normal range); 46 involved serum chemistry (abnormal liver function tests), three involved urinalysis and 11 involved tests of coagulation.

Discussion

Piperacillin sodium has been widely used in the treatment of severe lower respiratory tract infection (Mouton *et al.*, 1986), but its efficacy is now limited against some β-lactamase producing organisms, such as *S. aureus, H. influenzae, M. catarrhalis,* or hospital-acquired Gram-negative bacilli.

The two main strategies are used to deal with this problem of β-lactamase mediated antibiotic resistance: use of new β-lactam drugs able to withstand enzymatic inactivation; or combined administration of β-lactam antibiotics and β-lactamase inhibitors.

An example of the latter approach is use of the combination of piperacillin and tazobactam. The spectrum of activity of this combination extends to most of pathogens involved in pneumonia or bronchitis (Kuck *et al.*, 1989; Weiss *et al.*, 1989). Thus, it seems appropriate to test this combination in the therapy of lower respiratory tract infections and this was the purpose of this study.

The clinical response of the 133 clinically evaluable patients was impressive since the outcome was favourable in 127 patients (96%). The bacteriological response in the bacteriologically evaluable patients was also good since, at the early follow-up, only four of the 142 pathogens persisted. Moreover, all 15 piperacillin-resistant, piperacillin/tazobactam-susceptible pathogens were eradicated.

The overall incidence of adverse experiences in this trial was not unlike those reported for piperacillin alone and for other β-lactam antibiotics (Drusano, Schimpff & Hewitt, 1984). Piperacillin/tazobactam appears to be a safe and effective drug for the treatment of serious lower respiratory tract infection in hospitalized patients.

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