Piperacillin/Tazobactam vs Imipenem/Cilastatin in the Treatment of Nosocomial Pneumonia – a Double Blind Prospective Multicentre Study

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Abstract

Background: Piperacillin/tazobactam (P/T) with its broad spectrum of antibacterial activity is used widely for the treatment of moderate to severe polymicrobial nosocomial infections.

Patients and methods: The efficacy and safety of P/T was compared with imipenem/cilastatin (I/C) in patients with established nosocomial pneumonia. This multicentre study took place from January 1999 to December 2001. Due to difficulties in recruiting sufficient patients it was terminated prematurely. In all, 221 patients were randomly assigned to either P/T at 4 g/0.5 g (n = 110) or I/C at 1 g/1 g (n = 111). Additional aminoglycoside therapy was mandatory if *Pseudomonas aeruginosa* was present. The ITT population (107 P/T and 110 I/C patients) was used for the analysis of efficacy.

Results: The clinical efficacy was equally good for the P/T and I/C groups; 71% [95% CI 61.3, 79.2] vs 77.3% [95% CI 68.1, 84.5] at the end of therapy, 66.4% [95% CI 56.5, 75] vs 70% [95% CI 60.4, 78.2] on day 3, a nd 59.8% [95% CI 49.9, 69] vs 66.4% [95% CI 56.6, 74.9] on day 14 after therapy, respectively. Proven or assumed bacterial eradication at the end of therapy was 45.8% (P/T) and 52.7% (I/C). Treatment-related adverse events (AE) were recorded in 30% of P/T patients and 25.2% I/C patients. There were ten serious treatment-related AEs in the P/T group and five in the I/C group.

Conclusion: Although numbers were inadequate for full statistical evaluation, P/T and I/C were similarly effective in the treatment of severe nosocomially acquired pneumonia.

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Introduction

Pneumonia is the second most common nosocomial infection worldwide and is one of the leading causes of death [1–4]. Prevalence of nosocomial pneumonia within intensive care units in the US and Europe ranges from 10% to 65% with case fatality rates of more than 20% in a number of studies [5, 6]. Intubated patients are up to 21-fold more likely to develop nosocomial pneumonia than the patient without respiratory assistance [1, 7]. Nosocomial pneumonia requires prompt treatment and often before the causative organisms are identified [1, 5, 8, 9]. Identification in mechanically ventilated patients is hampered by the poor sensitivity and specificity of diagnostic methods [3, 10] and delaying therapy until the pathogens are identified may well be too late to influence survival [9]. Most episodes of inadequate empiric treatment are associated with *Pseudomonas aeruginosa, Acinetobacter* species, and *Staphylococcus aureus*, usually methicillin-resistant strains [5, 11] and the presence of P. aeruginosa, can lead to fatality rates of more than 40% [12].

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Piperacillin is an ureidopenicillin with excellent broad-spectrum activity against both Gram-negative and Gram-positive bacteria, and in combination with the betalactamase inhibitor tazobactam, it is stable to beta-lactamases produced by staphylococci, members of the *Enterobacteriaceae*, *Pseudomonas* species and anaerobes [7]. Thus piperacillin/tazobactam is highly appropriate for the treatment of nosocomial pneumonia [13]. *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae* and staphylococci (excluding methicillin-resistant strains) are highly susceptible to piperacillin/tazobactam [14, 15]. Some resistance is observed in *P. aeruginosa*, *Klebsiella*, *Acinetobacter*, *Enterobacter*, *Citrobacter* and *Serratia* species [5, 10, 11] and this is usually as a result of limited inhibition by tazobactam of the inducible chromosomally mediated Class 1 cephalosporinase produced by these organisms [15–17]. The fixed combination of piperacillin/tazobactam (dose ratio 8:1) has proved effective in the treatment of moderate to severe polymicrobial nosocomial infections, and has demonstrated equivalent or better efficacy than standard comparator regimens in these infections [14, 16, 18–22]. It is regarded as one of the core treatments for nosocomial infections in Germany and the US [2, 3, 10, 11]. There is however a need to provide further comprehensive and well controlled clinical studies to support the registration of piperacillin/tazobactam as a standard treatment for nosocomially acquired pneumonia [14].

A prospective, randomised, double blind multicentre Phase IIIb study was therefore undertaken in hospitalised patients with nosocomial pneumonia to confirm the efficacy and safety of piperacillin/tazobactam as monotherapy in the treatment of nosocomial pneumonia in Europe.

Patients and Methods

This study was carried out in 33 centres (26 in Germany, three in the Czech Republic and four in Hungary) between January 1999 and December 2001. The study was conducted in accordance with the Declaration of Helsinki and the European GCP/ICH guidelines The protocol was approved by the ethics committees at each centre and written consent from patients was obtained before commencing the study.

Study Design

Hospitalised patients with nosocomial pneumonia were randomly assigned to receive either piperacillin/tazobactam (4 g/500 mg) or imipenem/cilastatin (1 g/1 g) every 8 h according to a randomization schedule unknown to the investigator. If *P. aeruginosa* was present, additional aminoglycoside therapy was mandatory. Treatment lasted a minimum of 5 days (15 doses) but not more than 21 days (63 doses). Patients that were considered as not cured at the end of the 21st treatment day were assessed as therapy failures.

In order to maintain the study as investigator blind, the medication was prepared by a pharmacist who was not allowed direct contact with either the study patient or members of the nursing staff involved in the study and although the pharmacist remained in close contact with the investigator, the investigator was not informed about the treatment assigned to any patient or about the randomization code. The pharmacist was responsible for the preparation of dose-reduced infusion solutions for patients who developed renal insufficiency during the study and in order to keep the blind, the pharmacist was not allowed to reveal the identity of the administered study drug, unless there was an emergency.

Eligibility Criteria

The eligibility criteria were consistent between the different clinical centres. Male and female patients of at least 18 years of age were eligible for enrolment if they had a history as well as clinical and radiological evidence of pneumonia acquired 48 h or later after hospitalisation and also a new or evolving infiltrate on chest X-ray associated with pneumonia. The enrolled patients exhibited at least three of the following criteria, dyspnoea, purulent tracheal/bronchial sputum, body temperature 38 °C or < 36.1 °C (rectal, oral, or tympanic temperature), characteristic auscultation for pneumonia, leucocytosis (white blood cell count > 10,000/µl), C-reactive protein (CRP) greater than three times the upper limit of normal and identification of a causative pathogen.

Excluded from the study were patients who had participated in a clinical study within the last 30 days and who were pregnant or breast-feeding. Also excluded were patients who (1) were infected with piperacillin/tazobactam and/or imipenem/cilastatin-resistant pathogens; (2) had acute or chronic diseases (including immunosuppressive diseases) likely to interfere with patient compliance; (3) had cystic fibrosis, pulmonary malignancy, obstructive pneumonia, pulmonary abscess, empyema, active tuberculosis, bronchiectasis, or Pneumocystis carinii pneumonia; (4) had known or suspected concomitant viral, fungal, or parasitic infection requiring systemic treatment or known/suspected bacterial infection in addition to pneumonia (5) had received systemic antibacterial medication 24 h prior to study start, unless a respiratory culture showed that a pathogen was resistant to that agent (6) had any clinically significant central nervous system diseases or cardiac disorders, that would contraindicate the use of imipenem/cilastatin; (7) had concurrent haemodialysis, peritoneal dialysis, or plasmapheresis; (8) had exhibited the symptoms of shock within the last 48 h or who had a systolic blood pressure less than 90 mm Hg for more than 2 h; (9) had known or suspected hypersensitivity to the study medications and (10) had an APACHE II score < 8 or > 25.

Bacteriological Procedures

Two sets of blood cultures (for aerobic and anaerobic culture) were obtained before the study and during the treatment and post-treatment period and if a blood culture was clinically indicated according to the investigator. Cultures from the lower respiratory tract infection were obtained before (within 48 h) the study and during therapy (day 4), on the last day of therapy and at each of the post-treatment visit (3 and 14 days). The lower respiratory tract specimens obtained either by endotracheal aspiration, bronchoalveolar lavage (BAL), a protected brush procedure (PBP) or as sputum were required to show > 25 polymorphonuclear cells and < 10 squamous epithelial cells per field (at 100× magnification) and an organism on the Gram stain and in those obtained by BAL < 1% squamous epithelial cells with at least one pathogen. Isolates were cultured and tested for susceptibility to piperacillin/tazobactam and imipenem/cilastatin using current DIN or NCCLS guidelines [1, 14]. Each isolate was recorded as either a causative pathogen, contaminant or as part of the physiologic local fora. The causative pathogen was regarded as the isolate that was quantitatively dominant in each specimen.

Clinical and Bacteriological Assessment

The primary therapeutic objective was a comparison of clinical efficacy at 3 ± 1 days after the end of treatment (first follow-up). Clinical response was assessed in terms of production and characteristics of respiratory secretions, body temperature, need for mechanical ventilation/additional oxygen and lung radiography.

The secondary therapeutic analyses included clinical responses on the last day of treatment or on day 21 and on day 14 ± 7 days after treatment (second follow-up). Bacteriological responses were assessed for each evaluable patient at the first and second follow-ups and on the last day of treatment or on day 21. Bacterial susceptibilities were recorded as was the need for additional antimicrobial medication. Bacteriological outcome was characterised by standard definitions: (1) eradication, (2) presumed eradication, (3) persistence standard measure, (4) relapse, (5) superinfection, (6) colonisation, (7) eradication with and (8) not assessable.

Safety Assessment

Any patient who received at least one dose of study medication was included in safety evaluation. Safety was evaluated on the first and second follow-ups and comprised physical examination, assessment of clinical signs and symptoms and laboratory assessment of hematology and blood chemistry parameters.

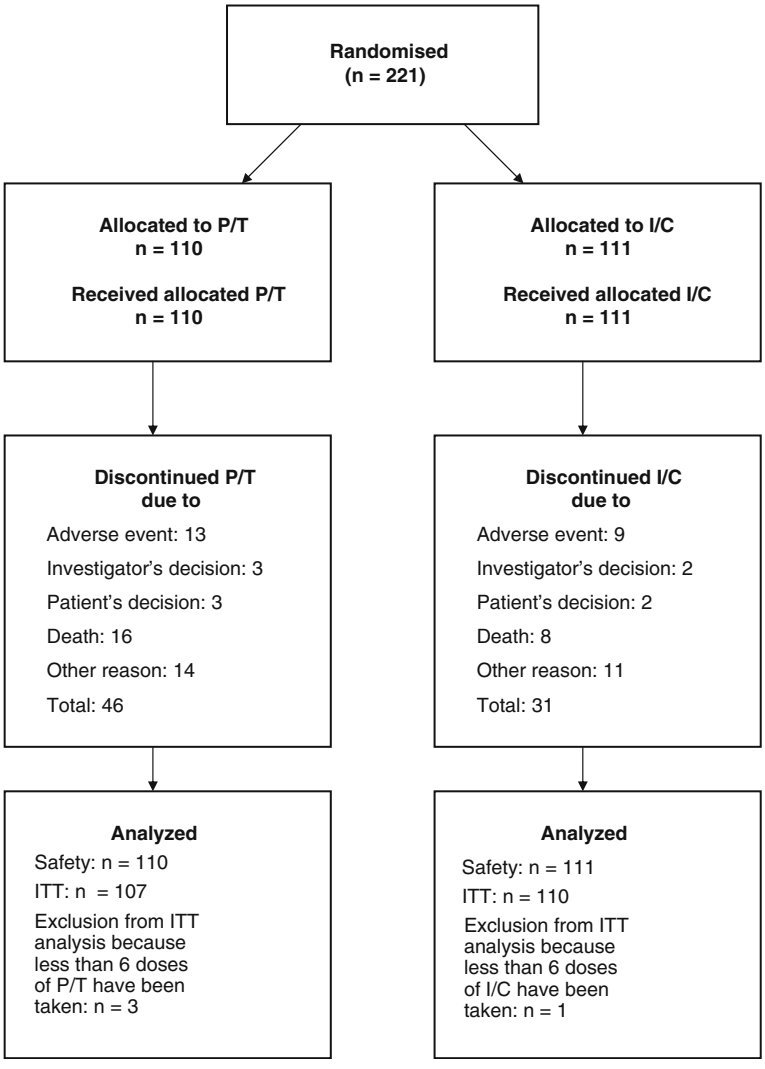

Figure 1. Study Plan.

Statistical Analysis

As the study was terminated prematurely it was decided before database closure and unblinding to analyse only demographic data, clinical and bacteriological efficacy and safety data. However, after unblinding the analyses were extended to include assessment of thoracic X-ray, core body temperature, leucocytosis, CRP and APACHE II score. In addition, 95% confidence intervals were calculated for the difference in response rates of clinical efficacy between the two treatment groups using the intent to treat populations.

Results

In all, 221 severely ill patients (piperacillin/tazobactam: 110 patients; imipenem/cilastatin: 111 patients) were enrolled. Safety was evaluated in the randomised patients. Clinical and bacteriological efficacy was assessed in the intent to treat population (ITT) which comprised patients who had received at least six doses of the study medication: 107 patients in the piperacillin/tazobactam group and 111 patients in the imipenem/cilastatin group (Figure 1).

The demographic and baseline characteristics of the two treatment groups of the ITT population differed only marginal (Table 1).

Baseline Microbiology

Prior to receiving the test medications, bacterial pathogens were cultured from the respiratory tract, blood and other sources in all patients (n = 221). The greatest number of pathogens was obtained from the respiratory system in both treatment groups (271 isolates compared with 50 blood isolates and 12 from other sources). The *Enterobacteriaceae* (n = 72) and *S. aureus* (n = 26) were the organisms most frequently isolated from the respiratory system in both treatment groups. None of the respiratory tract isolates was resistant to imipenem/cilastatin whereas an intermediate sensitivity or resistance to piperacillin/tazobactam was found for a minority of isolates (14/140) primarily members of the *Enterobacteriaceae* (n = 6) and *P. aeruginosa* (n = 4).

Clinical Response

Clinical outcomes, categorised either as response to treatment (cure/improvement), treatment failure or not assessable are shown in table 2 for the ITT population. At the first follow-up (3 ± 1 days after the end of treatment), the primary efficacy endpoint, a therapeutic response was seen in 66% [95% CI, 56.5%–75%] of patients receiving piperacillin/tazobactam

and in 70% [95% CI, 60.4%–78.2%] of patients receiving imipenem/cilastatin. Failure rates were similar at 18.7% and 18.2%, respectively.

Table 1
Demographic and baseline characteristics.

	Piperacillin/ tazobactam (n = 110)	Imipenem/ cilastatin (n = 111)
Age ± SD	68.4 ± 13.7	65.7 ± 13.8
Male/female	77/33	64/47
APPACHE II score	13.5 ± 4.2	13.3 ± 4.3
	Percentage of patients	**Percentage of patients**
Abnormal X-ray	98.2	99.1
Body temperature		
≥ 38 °C	67.3	67.6
36.1–37.9 °C	31.8	31.5
Leukocytosis	69.1	69.4
C-reactive protein		
≤ 15 mg/l	8.2	6.3
> 15 mg/l	79.1	83.6
Mechanical ventilation	28	19.1
Additional O_2 supply	73.8	75.5
Purulent / mucopurulent sputum	75.6	77.4

On the last day of treatment or on day 21, therapeutic responses were generally higher and seen in 71% [95% CI, 61.3%–79.2%] and 77.3% [95% CI, 68.1%–84.5%] of patients receiving piperacillin/tazobactam and imipenem/cilastatin respectively; failure rates were 17.8% and 16.4% respectively. At the second follow up (14 ± 4 days after the end of treatment) values wer e generally less at 59.8% [95% CI, 49.9%–69%] and 66.4% [95% CI, 56.6%–74.9%] and failure rates were 19.6% and 15%, respectively. The majority of patients in both groups responded to treatment and the overall response rate was higher in patients receiving imipenem/cilastatin, but there was overlap between confidence intervals indicating that the clinical response was similar for the two agents. Failure rates were also similar for the two treatment groups at each of the observation periods.

The numbers of patients in the piperacillin/tazobactam and imipenem/cilastatin groups who could not be assessed for clinical efficacy at the first follow-up, the primary efficacy endpoint, were 15.0% and 10.9% respectively. At the end of treatment or at 21 days, fewer patients were unassessable, 11.2% in the piperacillin/tazobactam and 5.5% in the imipenem/cilastatin group. As might be expected, the number of unassessable patients had increased at 14 ± 4 days after the end of treatment to 19.6% and 13.6%, respectively. The reasons for lack of assessment included (1) concomitant antibacterial therapy for a reason other than lack of efficacy, (2) concomitant antibiotic therapy for a proven infection other than pneumonia, (3) withdrawal of the patient after less than 48 h of therapy, (4) death not related to the underlying disease or (5) because an evaluation was not possible.

Table 2
Clinical efficacy of piperacillin/tazobactam and imipenem/cilastatin in patients with severe nosocomial pneumonia – ITT population.

	Piperacillin/tazobactam (n = 107)		Imipenem/cilastat in (n = 110)	
	n* (%)	**95% CI**	**n*(%)**	**95% CI**
Last day of treatment				
Response (cure/improved)	76 (71.0)	[61.3, 79.2]	85 (77.3)	[68.1 .5]
Treatment failure	19 (17.8)	–	18 (16.4)	–
Not assessable	12 (11.2)	–	6 (5.5)	–
First follow-up (3 days ± 1)				
Response (cure/improved)	71 (66.4)	[56.5, 75.0]	77 (70.0)	[60.4, 78.2]
Treatment failure	20 (18.7)	–	20 (18.2)	–
Not assessable	16 (15.0)	–	12 (10.9)	–
Second follow-up (14 days ± 4)				
Response (cure/improved)	64 (59.8)	[49.9, 69.0]	73 (66.4)	[56.6, 74.9]
Treatment failure	22 (20.6)	–	21 (19.1)	–
Not assessable	21 (19.6)	–	15 (13.6)	–

n: Number of patients in the specific group; n*: number of patients with data available; %: percentage of patients; CI: confidence intervals

Table 3
Respiratory tract secretions in response to treatment with piperacillin/tazobactam and imipenem/cilastatin in patients with severe nosocomial pneumonia – ITT population.

	Piperacillin / tazoctam (n = 107)		Imipenem/ cilastatin (n = 110)	
	n	%	n	%
Baseline				
Mucoid[a]		23.3		22.6
Mucopurulent	90	48.9	93	63.4
Purulent		26.7		14.0
Last day of treatment				
Mucoid		59.0		56.6
Mucopurulent	61	29.5	53	34.0
Purulent		9.8		9.4
First follow-up				
(3 days ± 1)		60.6		75.0
Mucoid	33	36.4	32	18.8
Mucopurulent		3.0		6.3
Purulent				
Second follow-up				50.0
(14 days ± 4)		53.5	20	35.0
Mucopurulent	15	40.0		15.0
Purulent		0		

n: Number of patients with respiratory secretions; [a]mucoid, clear and viscid without discolouration; mucopurulent, mucoid with some areas having discolouration characteristic of pus; purulent, pus – a thick yellowish or greenish fluid

Table 4
Bacteriological response to treatment with piperacillin/tazobactam and imipenem/cilastatin in patients with severe nosocomial pneumonia – ITT population.

	Piperacillin/ tazobactam (n = 107)	Imipenem/ cilastatin (n = 110)
	Percentage of patients	
Last day of treatment		
Proven eradication	14	13.6
Assumed eradication	31.8	39.1
Persistence	10.3	6.4
Superinfection	4.7	5.5
Not assessable[a]	36.4	31.8
First follow-up (3 days ± 1)		
Proven eradication	11.2	10.9
Assumed eradication	29	39.1
Persistence	5.6	3.6
Superinfection	4.7	3.6
Not assessable[a]	44.9	38.2
Second follow-up (14 days ± 4)		
Proven eradication	8.4	9.1
Assumed eradication	26.2	37.3
Persistence	2.8	2.7
Superinfection	4.7	4.5
Not assessable[a]	50.5	40.9

[a]Either because patients received concomitant antibacterial therapy for infection other than pneumonia, were withdrawn within 48 h after commencing the study or died during the study

At baseline, respiratory tract secretions were evident in 90 and 93 patients in the piperacillin/tazobactam and imipenem/cilastatin groups, respectively decreasing to 15 and 20 patients, respectively at the second follow-up (Table 3).

Only a minority of patients needed mechanical ventilation at baseline (30/107 and 21/110 patients in the piperacillin/tazobactam and imipenem/cilastatin treatment groups, respectively). The numbers of patients had decreased at completion of treatment, to 23/107 and 15/107 (three patients were missing in the latter group), respectively.

Bacterial Response

Overall eradication (proven and assumed) immediately after treatment with piperacillin/tazobactam or imipenem/cilastatin was 45.7% and 52.7%, respectively compared with 40.3% and 50% at the first follow-up and 34.6% and 42.2% at the second follow-up, respectively (Table 4). However, a number of patients could not be assessed for bacterial response in both treatment groups, 36.4% and 31.8% of patients at the end of treatment rising to 44.9% and 38.2% at the first follow-up and 50.5% and 40.9% at the second follow-up in the piperacillin/tazobactam and imipenem/cilastatin groups, respectively (Table 4). Reasons for lack of assessment included administration of concomitant antibacterial therapy for infection other than pneumonia, withdrawal within 48 h after commencing the study or death.

Rates of persistence were slightly higher in the piperacillin/tazobactam group, although the difference was minimal at the second follow-up. Overall superinfection rates were low, 3.6–5.5% and similar in both groups. Relapse was observed in one patient in the piperacillin/tazobactam group and two patients in the imipenem/cilastatin group at the first follow-up. At the second follow-up the numbers had increased in the piperacillin/tazobactam group to four patients.

Despite the clinical and bacteriological differences which tended to be in favour of imipenem/cilastatin, the patients in both treatment groups were treated for a comparable length of time; 23.6 single doses (± 9.4) of piperacillin/tazobactam and 24.3 single doses (± 9.3) of imipenem/cilastatin with an average duration of treatment of 8.7 (± 3.1) days and 9.0 (± 3.1) days, respectively.

Safety

All the randomised patients were included in the safety assessment. Overall 74.5% and 64.9% of patients receiving piperacillin/tazobactam and imipenem/cilastatin respectively reported adverse events, the majority of which were of mild intensity. The number of adverse events considered

Table 5
Most commonly reported treatment-related[a] adverse events (AEs) in the enrolled population.

Effects	Piperacillin/tazobactam (n = 110)		Imipenem/cilastatin (n = 111)	
	Percentage of patients	Number of AEs	Percentage of patients	Number of AEs
Diarrhoea	6.4	11	2.7	3
Nausea	1.8	2	3.6	4
Vomiting	0	0	3.6	4
Metabolic and nutritional disorders	4.5	5	8.1	11
Increased alkaline phosphatase	0	0	4.5	5
Immune system	3.6	4	1.8	2
Central and peripheral nervous system	2.7	5	0.9	2
Cardiac arrhythmias	2.7	3	1.8	2
Liver and gall bladder disorders	2.7	4	5.4	11
Thrombocytosis	2.7	3	2.7	3
Respiratory disorders	2.7	4	2.7	4

[a]Defined as definite or suspected – i.e. probable, possible, inaccessible or relationship missing (comprised 26.1% and 26.6% of all AE's)

Table 6
Serious adverse events (AEs) by body system in the enrolled study population.

Effects	Piperacillin/tazobactam (n = 110)		Imipenem/cilastatin (n = 111)	
	Percentage of patients	Number of AEs	Percentage of patients	Number of AEs
Cardiovascular failure	6.4	8	1.8	3
Respiratory system (insufficiency / pneumonia)	6.4	8	9.9	12
Heart rate and rhythm disorder – cardiac arrest	2.7	4	1.8	2
Bleeding/clotting disorders	2.7	4	0.9	1
Abnormal renal function	2.7	4	0	0
Extracardiac vascular disorders	1.8	2	1.8	2
Central and peripheral nervous system	0.9	3	1.8	3
Liver and biliary system	0.9	1	0.9	1
Myo-/endo-/pericardial and valve disorders	0.9	1	0	0
Neoplasm	0.9	2	0.9	1
Resistance mechanism disorders e.g. sepsis	0.9	1	1.8	2
Gastrointestinal system	0	0	0.9	1
All patients	22.7	43	18.9	30

to be related to treatment was similar in both treatment groups (piperacillin/tazobactam; 33/110 – 30% and imipenem/cilastatin; 28/111 – 25.2%). The most common related adverse events were diarrhoea and fever in the piperacillin/tazobactam group and increased alkaline phosphatase, nausea and vomiting in the imipenem/cilastatin group (Table 5).

The numbers of patients with at least one serious adverse event were 25 (22.7%) and 21 (18.9%) in the piperacillin/tazobactam and imipenem/cilastatin group, respectively, and the absolute number of serious adverse events was higher in the piperacillin/tazobactam group (43 vs 30) (Table 6). Serious adverse events with a possible relationship to study medication were recorded for four patients with ten serious adverse events in the piperacillin/tazobactam group and for four patients with five serious adverse events in the imipenem/cilastatin group.

More patients were withdrawn in the piperacillin/tazobactam group; 27/110 (24%) vs 15/111 (13.5%) in the imipenem/cilastatin group, but the majority of adverse events leading to a withdrawal of the patients were not related to treatment.

Overall there were 17 deaths in the piperacillin/tazobactam group and 11 deaths in the imipenem/cilastatin group, but only two deaths in the piperacillin/tazobactam group were assessed as possibly related to the medication. Pneumonia was involved in the death of one patient in the piperacillin/tazobactam group and two in the imipenem/cilastatin group.

The majority of patients did not show clinically relevant abnormalities in haematology (red blood cell and white blood cell counts), blood chemistry/arterial blood gas parameters in either treatment group.

Discussion

In this prematurely terminated study comparing piperacillin/tazobactam with imipenem/cilastatin, one of the standard treatments for nosocomially acquired pneumonia [1], clinical efficacy was similar in both treatment groups as was bacteriological efficacy and there were no treatment-related differences in rates of persistence, superinfection and relapse. The slightly poorer response for piperacillin/tazobactam compared with imipenem/cilastatin

may have been due to differences between the treatment groups in clinical isolates and the numbers of patients on mechanical ventilation at baseline. For example, antibacterial resistance was seen in 10% of respiratory isolates in the piperacillin/tazobactam group compared with no resistance in the imipenem/cilastatin group, *P. aeruginosa* was detected twice as frequently in patients receiving piperacillin/tazobactam and although mechanical ventilation was only required in the minority of patients in both groups, the numbers were greater in the piperacillin/tazobactam group (28% vs 19.1% imipenem/cilastatin group). The other difference which may have influenced outcome in favour of imipenem/cilastatin was the number of patients with fungal and/or viral infections who required topical or systemic antiviral and antifungal agents, 8.2% imipenem/cilastatin group compared with 12.1% in the piperacillin/tazobactam group. However the influence of these differences on clinical outcome is not clear. APACHE II overall severity scores were similar for piperacillin/tazobactam 13.4 ± 4.2 and imipenem/cilastatin 13.3 ± 4.3 and patients in both treatment groups were treated for a comparable length of time; 8.7 (± 3.1) days and 9.0 (± 3.1) days respectively. There was also a reduction in the numbers of patients on mechanical ventilation in both groups at the first and second follow-ups.

The overall clinical outcome was generally consistent with that of a previous comparative study with imipenem/cilastatin for the treatment of hospital-acquired pneumonia [1], although the clinical efficacy rates were higher for piperacillin/tazobactam than observed in the study reported herein; 83% compared with rates of 59.8–71.0%. Despite differences in efficacy rates, the treatment failure rates for piperacillin/tazobactam were similar for the two studies (17% vs 17.8–20.6%). The predominant pathogen was *P. aeruginosa* in the previous study (37%) [1], whereas in the study reported herein, the predominant pathogens were members of the Enterobacteriaceae (27%) and only 4% were *P. aeruginosa.* Resistance at baseline was however low in both studies and thus would not be likely to be related to any differences between the studies.

The efficacy and tolerability of piperacillin/tazobactam either as combination therapy with an aminoglycoside or as monotherapy is also similar to that observed for other typical therapeutic agents with or without aminoglycosides such as ceftazidime, amoxicillin/clavulanic acid and cefepimen in patients with nosocomially acquired pneumonia [7, 10, 23–26].

Despite the limitations of this study it may be concluded that piperacillin/tazobactam and imipenem/cilastatin were similarly effective in the treatment of severe nosocomially acquired pneumonia and although numbers were inadequate for full statistical evaluation. There were no major safety concerns with either piperacillin/tazobactam or imipenem/cilastatin and the adverse events observed were typical for these two therapeutic agents and similar to those reported in previous studies. These results support the use of piperacillin/tazobactam as a first line treatment in patients with nosocomially-acquired pneumonia.

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