Multicenter randomized trial comparing meropenem (1.5 g daily) and imipenem/cilastatin (2 g daily) in the hospital treatment of

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MULTICENTER RANDOMIZED TRIAL COMPARING MEROPENEM (1.5 G DAILY) AND IMIPENEM/CILASTATIN (2 G DAILY) IN THE HOSPITAL TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

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Summary: *An open, multicenter study with 144 patients, aged between 18 and 94 years, was performed to compare the efficacy and safety of meropenem with imipenem/cilastatin in the hospital treatment of community-acquired pneumonia. Patients were randomized to receive either intravenous meropenem (500 mg every 8 h) or intravenous imipenem/cilastatin (1,000 mg every 12 h). The primary end point was considered to be clinical efficacy and the secondary end points were bacteriological response and safety assessment. At the end of therapy, cure or improvement in signs and symptoms as a satisfactory clinical response was observed in 57 of 64 (89.1%) meropenem-treated patients and in 60 of 66 (90.9%) imipenem/cilastatin patients. The mean duration of treatment was 10 days for meropenem and 9.7 days for imipenem/cilastatin. In patients who were followed up for weeks 2-4, the response was satisfactory (100%) for both treatments. A satisfactory bacteriological response, defined as either presumed or confirmed eradication of all pathogens, was found in eight patients who had received meropenem and in 14 patients who had received imipenem/cilastatin. Response was considered satisfactory in 100% of the meropenem group and in 92.9% of the imipenem/cilas-*

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tatin group and at follow-up, it was 100% for both treatments. Drug-related adverse events were reported in three (4.2%) meropenem-treated patients and in eight (11.0%) imipenem/cilastatin-treated patients. None of these events was classified as serious. The results of this study show that the clinical and bacteriological efficacy and tolerability of meropenem (500 mg every 8 h) are similar to that of imipenem/cilastatin (1,000 mg every 12 h) in the hospital treatment of community-acquired pneumonia.

Introduction

Imipenem and meropenem are β-lactam antibiotics of the carbapenem group with a very broad spectrum of activity including most Gram positive cocci, Gram-negative bacilli and anaerobes (1-3). This feature makes carbapenems particularly useful for the empirical monotherapy of serious infections as well as for the therapy of cephalosporin resistant infections (4).

Imipenem, the first commercially available carbapenem, has to be coadministered with a dehydropeptidase inhibitor (cilastatin) to avoid extensive renal metabolism and nephrotoxicity (5).

Unlike imipenem, meropenem can be administered as a single agent without the need for coadministration of an enzyme inhibitor. In clinical studies both imipenem/cilastatin and meropenem have been successfully used in the treatment of a wide range of serious bacterial infections in inpatients (6-9).

The purpose of this study was to compare the clinical efficacy of 1.5 g daily of intravenous meropenem and 2 g daily of intravenous imipenem/cilastatin in the hospital treatment of community-acquired pneumonia. The drug dosages were chosen in accordance with product circulars and previous clinical trials. Secondary aims were to evaluate the bacteriological efficacy and the safety profiles of the two carbapenems.

Patients and methods

Patients. The design of this study was approved by the local Ethics Committee and written consent was obtained from all patients before participation in the study. Eligible for enrollment were patients of either sex, aged 18 years or older, who had been hospitalized for community-acquired pneumonia requiring treatment with an intravenous antibiotic. Diagnoses were made on the basis of specific signs and symptoms confirmed by chest X-ray. If pathogens were known at time of entry, they had to be sensitive to the allocated treatment.

Patients with hypersensitivity to any β-lactam antibiotics, as well as those with a history of seizures, fibrocystic disease, hepatic failure, hepatic coma or a neutrophil count $<1 \times 10^9$/l were not enrolled. Any patient who was terminally ill or had diseases or other conditions that might prevent completion of at least 48 h of therapy with the study drugs was excluded, as were pregnant or breast-feeding women. Other reasons for exclusion from the study were administration of any investigational drug within 30 days before enrollment or previous entry in the present study.

Patients who had received another antimicrobial agent in the previous 72 h were only included if there was bacteriological or clinical evidence that the previous treatment had been ineffective.

Treatment schedule. A separate, random scheme was generated for each center and patients satisfying the entry criteria were assigned to intravenous treatment with either meropenem or imipenem/cilastatin in a ratio of 1:1.

The meropenem (Zeneca, Milan, Italy) group received 500 mg every 8 h administered by intravenous injection over 5 min or by intravenous infusion over 15-30 min. The imipenem/cilastatin (Merck Sharp & Dohme, Rome, Italy) group was infused with 1,000 mg every 12 h according to the manufacturer's

recommendations. For renally impaired patients, the dose and frequency were reduced according to renal function. The duration of therapy depended on the severity of infection and on the patients' general condition. The recommended duration of therapy was 5-10 days and should have been limited to 28 days.

Clinical assessment. Before entry into the study a complete medical history was taken and a physical examination was performed. The severity of each of the signs and symptoms (dyspnea, cough, chest pain, emptysis, cyanosis and hypoventilation) was recorded as absent, mild, moderate or severe. The quantity of sputum and pleural effusion, the quality of sputum (categorized as mucoid, mucopurulent or purulent) and the presence of fever were assessed. The severity of infection, according to the classification of the attending physician, was globally evaluated as mild, moderate or severe.

Clinical monitoring of patients was performed before treatment, after 3-5 days, after 8-10 days (and once every 5 days) after starting treatment, within 3 days after stopping and, whenever possible, between 2-4 weeks after treatment. The radiological examination was performed at entry to the study, after the end of treatment (within 3 days) and at follow-up.

Changes in the clinical symptoms of infection were used to assess the clinical efficacy of the treatment using the following criteria: i) cure: complete remission of all systemic and local signs and symptoms of infection without association of other antibiotics apart from the study drug; ii) improvement: attenuation of all systemic and local signs and symptoms without complete remission; iii) unchanged or worse: no improvement or deterioration of signs and symptoms; iv) relapse: initial cure or improvement at the end of therapy, followed by a general decline and worsening of the clinical condition at follow-up. Both cured and improved patients were considered as satisfactory clinical responses while unchanged, worse, or relapsing patients indicated treatment failure.

Patients were considered unevaluable in the following cases: misdiagnosed patients, violators of entry criteria, those receiving treatment for less than 48 h or those receiving concomitant antibiotics after 48 h of therapy with the study drug or between the end of therapy and the follow-up assessment.

Bacteriological assessment. Respiratory samples were obtained for Gram staining and microbiological culture before therapy and, where possible, during and after completion of treatment. Organisms were isolated and identified by a standard microbiological method. Disc susceptibility testing using the Kirby Bauer method (10) or minimal inhibitory concentrations were performed on all isolates with susceptibility reported in the National Committee for Clinical Laboratory Standards (11). To be microbiologically evaluated, sputum samples needed to contain <10 epithelial cells and >10 polymorphonuclear leukocytes/field (12). Blood and urine cultures were also performed.

Bacteriological response was evaluated at the end of therapy and follow-up assessment and was defined according to the following classification: i) success: eradication of the original primary pathogen(s); ii) presumed success: no further culture was available due to clinical cure or improvement; iii) partial success: eradication of one or more, but not all, of the original organisms of a polymicrobial infection; iv) failure: persistence of causative organism(s). Success and presumed success were considered as satisfactory responses.

Tolerability and safety assessment. Tolerability and safety variables included monitoring of clinical and laboratory events. All adverse events were assessed for time of onset, duration, intensity (mild, moderate, or severe), severity, relationship to the study drug (definitely, probably, probably not, definitely not, or undetermined) and outcome.

The laboratory tests included complete urinalysis and the following clinical chemistry and hematological para-

meters: hemoglobin, hematocrit, white blood cell and red blood cell count, serum creatinine, total bilirubin, total serum protein, blood glucose, blood urea, serum albumin, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase. Laboratory samples were collected before treatment, after 3-5 days of treatment, at least once every 5 days during treatment and within 3 days of stopping treatment. Weekly follow-ups were done if a significant abnormality was detected and were continued until the variable returned to normal or to pretreatment values.

Methods of analysis. The comparison between groups was performed with the uncorrected chi-square test, estimating the difference in proportion between treatment groups and the relevant 95% confidence interval using the normal approximation. Symptoms and signs were compared between treatments with the two-tailed Mann-Whitney U-test.

Results

Patients. The study was performed between 1995 and 1997. Twelve centers recruited a total of 144 patients: 71 patients were randomly assigned to receive meropenem and 73 to receive imipenem/cilastatin.

Table I summarizes the essential baseline characteristics of the monitored patients. None of the patients needed to be housed in an intensive care unit.

Clinical efficacy. At the end of treatment assessment, 64 of the 71 patients in the meropenem-group

Table I *Baseline characteristics*

Patient characteristics	Meropenem group Number (%) of patients	Imipenem/cilastatin group Number (%) of patients
Demographic factors		
Males	43 (61%)	54 (74%)
Females	28 (39%)	19 (26%)
Age <60 years	35 (49%)	37 (51%)
Age >60 years	36 (51%)	36 (49%)
Ethnic group		
Caucasian	68 (96%)	70 (96%)
Afro Caribbean	2 (3%)	1 (1.4%)
Asian	1 (1.4%)	2 (3%)
Host factor		
Cigarette smoking	21 (30%)	28 (38%)
Obstructive pulmonary disease	12 (17%)	20 (27%)
Physical examination findings		
Pretreatment temperature >38.3 °C (101.0 °F)	18 (25%)	27 (37%)
Dyspnea	39 (55%)	40 (55%)
Chest pain	32 (45%)	35 (48%)
Bloody sputum	8 (11%)	4 (5%)
Pleural effusion	12 (17%)	9 (12%)
Laboratory findings		
White blood cell count outside upper limit	28 (39%)	36 (49%)

and 66 of the 73 patients in the imipenem/cilastatin group were clinically evaluable. Seven patients in the meropenem group were excluded from clinical evaluation (four presented an incorrect diagnosis, one patient died and two patients withdrew for other reasons). Seven patients in the imipenem/cilastatin group were excluded (two were misdiagnosed, one had pretherapy resistant pathogens and four patients withdrew for other roasons).

Treatment with meropenem lasted 4-20 days (mean 10 days) and treatment with imipenem/cilastatin lasted 4-16 days (mean 9.7 days). Radiological examination normalized or improved in 52 of 57 (91.2%) patients in the meropenem group and in 53 of 59 (89.8%) patients in the imipenem/cilastatin group. Temperature was normalized in 50 of 59 (84.7%) patients in the meropenem group and in 50 of 61 (81.9%) patients in the imipenem/cilastatin group. Mean time to normalization was 2.7 days for the meropenem group and 3.2 days for the imipenem/cilastatin group.

The clinical response was classed as satisfactory (cure or improvement) for 57 (89%) patients treated with meropenem and for 60 (91%) treated with imipenem/cilastatin (Fig. 1). Seven patients treated with meropenem and six patients treated with imipenem/cilastatin were considered to be clinical failures.

At follow-up assessment between 2-4 weeks after the end of treatment, the clinical response was evaluable in 36 patients from the meropenem group and in 32 from the imipenem/cilastatin group. At this time no relapse was recorded and 100% of patients were classed as having responded satisfactorily to the therapy (Fig. 1).

Bacteriological efficacy. The number of bacteriologically evaluable patients at the end of therapy was eight out of 64 clinically evaluable patients in the meropenem group and 14 out of 66 in the imipenem/cilastatin group. Patients were bacteriologically not evaluable mainly because of failure to isolate a pathogen from a valid pretreatment sample.

All pretreatment blood and urine samples were negative for the presence of pathogens. Microorganisms were isolated from sputum (26 times),

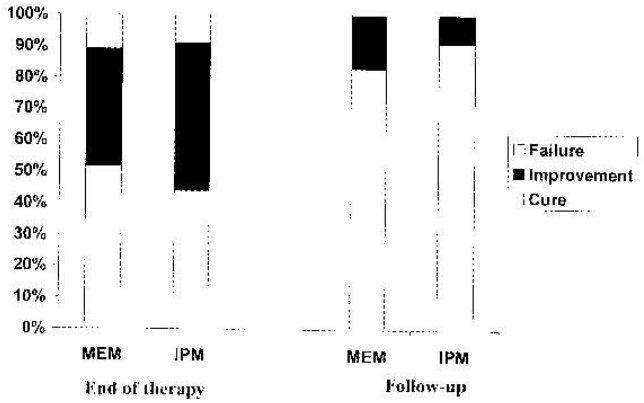

Fig. 1 Clinical responses at end of therapy and at follow up.

from aspirate from tracheotomy (seven times) and from bronchial aspirate (once) from 22 patients (eight in the meropenem group and 14 in the imipenem/cilastatin group). Four patients (one in the meropenem group and three in the imipenem/cilastatin group) had polymicrobial infections.

Fourteen pathogens were Gram-positive (seven *Streptococcus pneumoniae* and seven *Staphylococcus aureus*) and thirteen were Gram-negative (four *Pseudomonas aeruginosa*, two *Haemophilus* species, one *Haemophilus influenzae*, and another six were Gram-negative bacteria) (Fig. 2). Eradication or presumed eradication at the end of treatment was recorded in all patients (100%) in the meropenem group and in 13 of 14 patients (92.9%) in the imipenem/cilastatin group. The patient who failed to respond bacteriologically and clinically to the treatment with imipenem/cilastatin had a polymicrobial infection with *S. aureus* and *P. aeruginosa* isolated from tracheotomy aspirate. While *S. aureus* isolate was susceptible to imipenem/cilastatin, *P. aeruginosa* showed an intermediate susceptibility. This strain was resistant to meropenem.

At follow-up assessment six patients in the meropenem group and five in the imipenem/cilastatin group were bacteriologically evaluable. The satisfactory response rate was 100%, both in the meropenem group and in the imipenem/cilastatin group.

Tolerability and safety. Of 144 patients, 20 of 71 (28%) in the meropenem group and 15 of 73 (20%) in the imipenem/cilastatin group suffered adverse events. However, in the investigator's judgment, five events in three patients (4.2%) in the meropenem

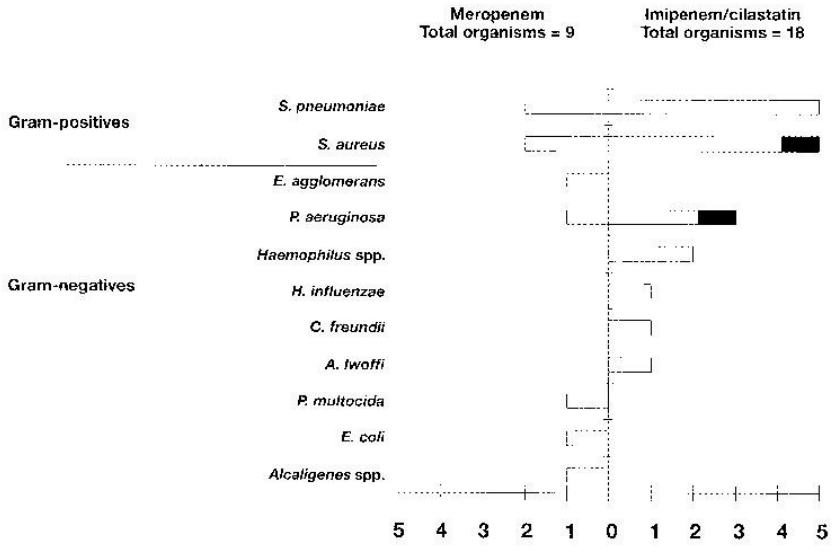

Fig. 2 Pathogens isolated from patients in the meropenem group (MEM) (n = 8) and in the imipenem/cilastatin group (IPM) (n = 14). Pathogens not eradicated ■.

group and 11 events in eight patients (11%) in the imipenem/cilastatin group were definitely or probably related to the applied treatment. With meropenem, there was one occurrence each of increased hepatic enzymes, decreased red blood cells, thrombocythemia, leukopenia and decreased albumin as potentially drug-related events. With imipenem/cilastatin, the events were two each of decreased hematocrit, decreased red blood cells, thrombocythemia, leukopenia and one each of increased hepatic enzymes, decreased albumin and exanthema (Table II). None of these events was classified as serious. The severity was mild in the meropenem group, and in the imipenem/cilastatin group, it was mild in eight and moderate in four. All events, except for one with imipenem/cilastatin, which was reported as still ongoing at the last observation, were reversible. A drug related adverse event led to treatment withdrawal of one patient in the imipenem/cilastatin group. He suffered from exanthema, not reported as serious by the investigator, but withdrew after 9 days of therapy (17 doses of intravenous infusion). The patient recovered from the event. One death occurred during the study treatment. A patient died in the meropenem group due to cardiovascular collapse on the fourth day of therapy after 10 x 0.5 g doses. There was no causal relationship between the study drug and the death.

There was no statistical evidence that either medication was associated with a greater incidence of adverse events, although the proportion of patients experiencing potential drug reactions with meropenem was less than half of that with imipenem/cilastatin.

Discussion

The results of this multicenter study indicate that the clinical and bacteriological efficacy of meropenem (1.5 g daily, 500 mg every 8 h) and that of imipenem/cilastatin (2 g daily, 1 g every 12 h) were equivalent in the hospital treatment of community-acquired pneumonia, with a high success rate seen in both groups at treatment end and at follow up. The two carbapenems also showed equivalent tolerability and safety.

Community acquired pneumonia is a common and important therapeutic problem in medical practice. Most cases are mild but mortality among inpatients is 5-20% (13). Most patients are treated empirically because a definite etiologic diagnosis is not made in up to 50% of cases (14, 15) or because the diagnosis is not available for 24-48 h, or even for several weeks if confirmed by serology (16). Moreover, the rational choice of an antimicrobial agent requires knowledge of the epidemiology of

Table II *Drug related adverse events*

Adverse events	Meropenem group Number of patients	Imipenem/cilastatin group Number of patients
Laboratory events		
Leukopenia	1	2
Red blood cell decrease	1	2
Thrombocythemia	1	2
Albumin decrease	1	1
Hepatic enzymes increase	1	1
Hematocrit decrease	—	2
Clinical events		
Exanthema	—	1

infections, as well as assessment of the clinical presentation and severity of the disease (17).

Guidelines to help physicians in the selection of drugs for the initial treatment of community-acquired pneumonia were published in 1993 by the American Thoracic Society, the British Thoracic Society and the Canadian Infectious Disease Society (18-20). Recently, guidelines for the management of immunocompetent adult patients with community-acquired pneumonia were also published by the Infectious Disease Society of America (21). These were produced taking into account three factors: patients' age, the presence of underlying disease and the severity of the pneumonia itself. As far as inpatients (excluding those at risk for HIV infection) are concerned, the recommended empirical regimen includes a second or third generation cephalosporin or β-lactam/β-lactamase inhibitor combination, either with or without a macrolide. For non-HIV inpatients with severe community-acquired pneumonia, the recommended therapy is a macrolide plus a third-generation cephalosporin with antipseudomonal activity, or other antipseudomonal agents such as carbapenems or fluoroquinolones. This wide spectrum antibiotic coverage is directed to *S. pneumoniae, Legionella pneumophila* and Gram-negative bacilli, including *P. aeruginosa*.

In our study imipenem/cilastatin and meropenem were used as monotherapy for the hospital treatment of community-acquired pneumonia. The two carbapenems showed similar clinical efficacy both at the end of treatment (89% for meropenem and 91% for imipenem/cilastatin) and at the follow-up assessment (100% for both drugs).

Only 17% of patients had microbiologically documented infections identified by microbiological procedures, confirming the difficulty of obtaining a definite etiologic diagnosis of community-acquired pneumonia. The pathogens isolated were *S. pneumoniae, S. aureus, P. aeruginosa, Haemophilus* spp. and other Gram-negative bacilli. A satisfactory bacteriological response was attained in 100% of patients in the meropenem group and in 93% of patients in the imipenem/cilastatin group at the end of treatment and in 100% of patients in both groups at follow-up. This favorable result reflects the excellent activity of carbapenems against bacteria that commonly cause community-acquired pneumonia, including problematic pathogens such as *P. aeruginosa*. In this study *P. aeruginosa* was considered responsible for 15% of the microbiologically documented cases and it was involved in the only documented case of bacteriological and clinical treatment failure with imipenem/cilastatin. Since the study protocol did not include serological assays, it was not possible to evaluate the etiologic role of microorganisms such as *Legionella* spp., *Mycoplasma pneumoniae, Chlamydia* spp., *Coxiella burnetii* or viruses.

Both carbapenems were well tolerated, confirming their good tolerability profile. Minor and transient drug-related changes in laboratory values were observed in only 4% of the meropenem-treated patients and in 11% of the imipenem/cilastatin-treated patients. Only in one patient in the imipenem group was a clinical adverse event (exanthem) observed which, while not considered serious, led to the patient's withdrawal from the study. No cases of nausea, vomiting or inflammation of the site of infection were reported in patients receiving meropenem by bolus injection or by intravenous infusion or in those receiving intravenous infusion of imipenem/cilastatin according to the manufacturer's recommendation. Our findings are not in accordance with the higher incidence of these adverse effects in patients receiving imipenem/cilastatin than in those receiving meropenem, which has been observed in previous studies (22). This confirms the relationship between the occurrence of these symptoms and the rapid infusion as well as the dosage of imipenem/cilastatin (23-25).

In conclusion, the results of this study show that empirical monotherapy with meropenem, even at a

lower dosage (1.5 g daily), is as effective and well tolerated as that with imipenem/cilastatin (2 g daily) in the hospital treatment of community-acquired pneumonia. Carbapenems are valid candidates for use in the hospital treatment of community-acquired pneumonia when no etiologic diagnosis has been made and when multiply resistant pathogens, such as *Klebsiella spp.*, *Proteus spp.* and *P. aeruginosa* are suspected. This problem mainly concerns the elderly, patients with underlying illnesses and those in whom previous therapy with other β-lactam antimicrobials has failed.

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