Treatment of Nosocomial Pneumonia: An Experience with Meropenem

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This study aimed at evaluating the efficacy and safety of meropenem as first choice treatment for nosocomial pneumonia (NP) in intensive care units (ICU) in Hospital das Clínicas (HC) - University of São Paulo; a hospital with high incidence of antimicrobial resistance. Prospective, open, and non-comparative trial with meropenem were done in patients with ventilator-associated or aspiration NP in 2 ICUs at HC – University of São Paulo. Etiologic investigation was done through bronchoalveolar lavage and blood cultures prior to study entry. Twenty-five (25) critically ill patients with NP were enrolled (mean age 40 years). Ventilator-acquired pneumonia was responsible for 76% of cases and aspiration NP for 24%. Specific etiologic agents were identified and considered to be clinically and temporally responsible for NP in 11 (44%) patients. *A. baumanii* was responsible for 6 cases (55%), *P. aeruginosa* for 3 (27%), and *S. aureus* for 2 (18%). At completion of treatment, 19 patients (76%) showed either cure (48%) or improvement (28%) after use of meropenem therapy. Mortality was 12% at the end of therapy (8% after excluding 1 non-evaluable patient). After 4 to 6 weeks of follow-up, 12 (48%) patients had improved or been totally cured, and overall mortality was 24%. Clinical complications were observed in 11 patients (44%), with none of them definitely related to the study drug. Meropenem as monotherapy was effective and well-tolerated in most NP patients in our ICU. The low mortality rate in this study might have been due to first choice use of this drug. Controlled, drug comparative clinical trials are needed to support this preliminary observation.
Key Words: Meropenem, nosocomial pneumonia, intensive care unit.

It is well known that multi-resistant bacterial strains are increasingly prevalent in hospital environments. Bacterial resistance is an important problem to be faced especially by practitioners in Intensive Care Units (ICUs) worldwide.

Increasing, and sometimes inappropriate, antibiotic therapy has resulted in a higher incidence of resistant bacteria that may be difficult to treat. This, coupled with a rising number of debilitated patients, means that the need for correct use of antibiotics and for careful clinical and microbiological studies has never been greater.

The development of new drugs may also be a priority in these circumstances. Research has been done with many different classes of antibiotics and the carbapenems, which are broad-spectrum β-lactam antibiotics, are among those of greatest interest.

Meropenem is the first of a new class of dehydropeptidase-stable carbapenem antibiotics [1]. It is highly active against a wide spectrum of pathogenic bacteria [2], including Gram positive and Gram negative microorganisms and anaerobes. Despite its lack of activity against *Staphylococcus sp* resistant to methicillin, *Enterococcus faecium*, *Enterococcus faecalis*, *Streptococcus pneumoniae* with high level resistance to penicillin, and *Stenotrophomonas maltophilia*; meropenem has been shown to be effective against strains of *Enterobacteriaceae*, *Pseudomonas spp*, and Acinetobacter *spp* resistant to third generation cephalosporins, quinolones and aminoglycosides [3].

Meropenem has been shown to be effective in treating a range of infections in experimental animal models [4], and has shown good safety and efficacy in clinical trials in patients with nosocomial infections [18, 19], including those caused by multi-resistant bacterial strains [5, 17].

Pneumonia is the second most common nosocomial infection [4], accounting for 13% to 18% of all hospital infections [6]. Nosocomial pneumonia (NP) occurs in 5% to 10% of hospital admissions [3, 7, 13] and this rate increases 6 to 20 times in mechanically ventilated patients [20]. The crude mortality rates for hospital pneumonia range from 20% to 70% [2, 6, 13], probably due to the severity of underlying diseases in the population studied. In contrast, attributable mortality due to pneumonia has been estimated as 30% to 50% [6, 11, 13].

Clinical diagnosis of NP is based on the presence of a new radiological pulmonary infiltrate [10] in a patient with 2 of the following criteria: purulent sputum, fever or hypothermia, leukocytosis, or leukopenia [13]. For mechanically ventilated patients, clinical criteria for the diagnosis of pneumonia lack specificity, thus leading to controversy over the benefits and risks of using more specific and invasive diagnostic methods [6, 13].

Etiological agents can be isolated by bronchoalveolar lavage (BAL) and/or protected specimen brush (PSB) with 85% to 100% sensitivity and 95% to 100% specificity [6]. As bronchoscopy is an invasive technique and not always available, nonbronchoscopic or "blind" BAL appears to provide reliable results [15]. Blood cultures can provide a specific diagnosis in patients with bacteremia. Gram's stain or culture of pleural fluid are specific, but can only be performed in a small number of patients [6, 13].

The main causative agents in NP are aerobic Gram-negative bacilli (*Enterobacteriaceae*, *Pseudomonas spp*, *Acinetobacter spp*). They have been implicated in 20% to 60% of reported cases [6, 13]. *Staphylococcus aureus* is responsible for 20% to 40% of cases, and anaerobes in 0% to 35% of cases. Community agents like *Streptococcus pneumoniae* and *Haemophilus influenzae* are generally involved in early onset (< 5days) bacterial pneumonia [6, 7, 13].

This study sought to evaluate the efficacy and safety of meropenem as the first choice treatment for respirator-associated and/or aspiration nosocomial pneumonia in the ICU at Hospital das Clínicas - University of São Paulo; a major tertiary hospital with a high prevalence of antimicrobial resistance.

Secondary aims were to evaluate bacteriological efficacy of meropenem and to assess the safety and tolerance of meropenem, as measured by the incidence of adverse events and the effects on appropriate hematological and biochemical variables.

Materials and Methods

This was a prospective, open, non-comparative trial with meropenem in ventilator-associated or aspiration nosocomial pneumonia. Twenty-five (25) patients were recruited at 2 intensive care units at the Hospital das Clínicas - University of São Paulo between April, 1997, and September, 1998.

Patients aged 18 years or older were included. Written and/or witnessed informed consent to participate in the trial was taken prior to initiating the study. Comatose patients were included only after the informed consent was obtained from a legally responsible relative. Patients eligible for inclusion were necessarily hospitalized with the presence of new radiological pulmonary infiltrate, purulent sputum, and signs of sepsis, thus requiring a parenteral antibiotic. Clinical categories included were aspiration pneumonia and ventilator-associated pneumonia according to classifications in the *Guidelines for Prevention of Nosocomial Pneumonia* [7]. Patients with previous broad spectrum antibiotic therapy were included only if bacterial isolates were resistant to them and susceptible to carbapenems. If multiple pathogens were present at entry, at least 1 isolate must have been susceptible to the study drug. Patients using narrow spectrum penicillin to community acquired infections, anti-tuberculous drug, or anti-toxoplasmic therapy were also included.

Patients were excluded from the study if any of the following criteria was found: pregnancy or breast feeding; hypersensitivity to any β-lactam; another

investigational drug given within 30 days prior to study entry; severe hepatic impairment, such as hepatic failure or hepatic coma; neutropenia (neutrophil count <1000 cells/mm³); cystic fibrosis; previous trial entry; patient unlikely to complete at least 48 hours of trial drug treatment; previous treatment with a potentially effective antibiotic within the last 24 hours prior to treatment, unless the microorganism was shown to be resistant or was still present and susceptible to carbapenems.

Meropenem was given intravenously in bolus at a dose of 1 g every 8 hours, due to the high prevalence of resistant microorganisms in the study environment and, thus, the high possibility of *P. aeruginosa* and *Acinetobacter* sp infections. Dose adjustments were made in patients with impaired renal function, according to prescribing information. Duration of treatment depended on the clinical and bacteriological presentation, however a treatment duration period of 5 to 21 days was established for all patients.

Etiological investigation was done through bronchoalveolar lavage (bronchoscopic or "blind") and blood cultures prior to study entry. Pleural fluid culture was obtained and considered diagnostic when indicated. Subsequent per- and post-treatment cultures were done according to clinical needs.

Clinical assessments were done pre-, per- and post-treatment period, including a general physical examination, laboratory and chest radiographic evaluations. Follow-up evaluations were done in most patients at 4 to 6 weeks after the completion of treatment.

Laboratory blood evaluation included hemoglobin, hematocrit, WBC, platelet count, serum creatinine, total bilirubin, albumin, alkaline phosphatase and hepatic enzymes (SGOT and SGPT).

After clinical, microbiological, laboratory and chest radiographic assessments, patients were classified into 5 different categories according the overall response at the end of treatment and follow-up evaluation: cure; improvement; failure; relapse; and not evaluable.

Data analysis was descriptive, with the results resumed in tables of frequency. The numeric variables were presented as mean, variance, and standard deviation.

Results

The study was conducted in 2 ICUs at the HC – University of São Paulo, between April, 1997, and September, 1998. Twenty-five (25) critically ill patients with nosocomial pneumonia (NP), aged 18 to 77 (mean 39.9) were enrolled. Sixteen (64%) were male (Table 1). Ventilator-acquired NP was responsible for 76% of cases and aspiration NP occurred in 24% of patients.

Underlying diseases were: tetanus (8); AIDS plus opportunistic infection (6); leptospirosis (4); neurological diseases (3); measles plus encephalitis (1); severe malaria (1); rheumatic disease, with longterm steroids (1); staphylococcal sepsis (1) (see Table 1). Eighteen (72%) presented some degree of conscious impairment.

Eleven patients (44%) were using narrow spectrum antibiotics for underlying diseases at the time of inclusion: 8 were receiving penicillin G for tetanus (5), or leptospirosis (3); 3 were taking oxacillin to treat tetanus focus; and 2 were being treated for tuberculous or toxoplasmic CNS infections. Five patients (20%) were using another broad spectrum antibiotic but the microorganism was shown to be resistant or still present at the time of inclusion.

Etiological agents were isolated in 14 patients (56%), though only 11 (44%) were considered clinically and temporally responsible for the NP. *A. baumanii* was the etiological agent in 6 cases (54.5%), with an 83.3% rate of sensitivity to meropenem. *P. aeruginosa* was the etiological agent in 3 cases (27.3%), though the susceptibility was tested in only 1 isolate. *S. aureus* was the etiological agent in 2 cases (18.2%), 1 case susceptible to meropenem.

Twelve patients developed infection at a new site during meropenem therapy, requiring the addition of another drug as follows: 8 received vancomycin (6 *S. aureus* bacteremia, 1 *E. faecalis* bacteremia, and 1 empirical); 5 (20%) received amphotericin B preceded or not by fluconazole for *Candida sp* urinary infections (4) or abdominal sepsis (1); 1 (4%) received gentamicin for *E. faecalis* bacteremia.

At the completion of treatment, 19 patients (76%) showed cure (48%) or improvement (28%) with meropenem therapy. Mortality was 12% at the end of

Table 1. Outcome of nosocomial pneumonia treated with meropenem according to age, underlying disease, and etiologic agent

Patient number	Age	Underlying disease	Pneumonia etiology	Adverse event	End of treatment	Follow-up 4 to 6 wks
1	48	*S. aureus* sepsis	*A. baumanii* *S. aureus*	Hypotension and coronary spasm, hypercalemia	Improvement	Death **
2	59	Neurological disease	*E. cloacae* *A. baumanii*		Cure	Cure Relapse
3	23	Tetanus	*P. aeruginosa*		Cure	Cure
4	28	Leptospirosis	Not isolated	Cutaneous rash, seizures	Cure	Cure
5	38	Severe malaria	Not isolated	Gastritis	Cure	Cure
6	37	AIDS and sepsis	*S. aureus*		Cure	Not available
7	22	Measles encephalitis	Not isolated		Cure	Cure
8	50	AIDS and hepatocellular carcinoma	Not isolated		Cure	Death **
9	56	AIDS and cerebral toxoplasmosis	Not isolated	Adrenal failure and shock	Death ♠♠	Death ♠♠
10	26	Neurological disease	Not isolated		Improvement	Death **
11	36	Leptospirosis	Not isolated	Liver enzyme increase	Cure	Cure
12	42	Tetanus	*A. baumanii* *P. aeruginosa*		Failure	Failure
13	44	Tetanus	Not isolated		Cure	Cure
14	48	Tetanus	*S.* coagulase - *A. baumanii*		Failure	Failure
15	45	AIDS and cerebral toxoplasmosis	*A. baumanii*	Pulmonary embolism	Death ** <12 h	Death **
16	39	Tetanus	Not isolated		Improvement	Cure Relapse
17	46	Tetanus	Not isolated	Anemia	Cure	Cure
18	43	AIDS and encephalitis	Not isolated	Cutaneous rash	Improvement	Improvement
19	39	Tetanus	Not isolated		Cure	Cure
20	39	Leptospirosis	Not isolated		Cure	Cure
21	40	AIDS and renal failure	*P. aeruginosa*		Improvement	Death ♠♠
22	31	Rheumatological	*Enterobacter cloacae*		Failure	Death ♠♠
23	24	Neurological disease	*S.* coagulase - *A. baumanii*	Liver enzyme increase	Improvement	Relapse
24	77	Tetanus	*H. influenzae*	Severe hemorrhage	Death **	Death **
25	18	Leptospirosis	Not isolated	Renal failure	Improvement	Cure

** Related to the underlying disease. ♠♠ Secondary to failure.

therapy, though 1 patient died of pulmonary embolism within 12 hours of meropenem therapy. (end of therapy mortality was 8.5% after excluding this non-evaluable patient). After 4 to 6 weeks of follow-up, 12 (48%) patients had improvement or total cure of NP, and general mortality was 24%.

Although clinical complications were observed in 11 patients (44%), none of them were definitely related to the study drug. Five patients presented severe complications (20%): 4 were probably related to underlying disease (hypotension, coronary spasm and hypercalemia in a septic diabetic patient; shock and adrenal failure in 1 terminal AIDS patient; pulmonary embolism; hemorrhagic shock in an anticoagulated patient) and 1 secondary to infection at a new site (septic shock). Six patients (24%) showed mild adverse events, 2 probably associated to the underlying disease, and 3 possibly related to meropenem (skin rash, seizure, and gastritis).

Discussion

Pneumonia is the second most common nosocomial infection and is associated with substantial morbidity and mortality. The majority of adult patients with hospital acquired pneumonia have severe underlying diseases, immunosuppression, depressed sensorium and/or cardiopulmonary diseases.

Preventive measures for hospital pneumonia include decreasing aspiration by the patient, preventing cross-contamination or colonization via hands of personnel, appropriate disinfection or sterilization of respiratory therapy devices, use of available vaccines to protect against particular infections, and education of hospital staff and patients [4].

Accurate diagnosis of NP is critical to avoid the inappropriate use of antibiotics and the development of antibiotic resistant bacterial populations. The main agents are the aerobic Gram-negative bacilli, *Staphylococcus aureus* and anaerobes [6, 13]. Community agents, like *Streptococcus pneumoniae* and *Haemophilus influenzae*, can be involved [6, 7, 13].

Hospital das Clínicas is one of the biggest university hospitals in Brazil. Due to its size, a characteristic flora composes its micro-environment; with Gram negative bacilli mostly resistant to third generation cephalosporines, aminoglycosides and quinolones; and *Staphylococcus aureus* mostly only sensitive to vancomycin and teicoplanin.

Meropenem is the second commercially available carbapenem with a broad anti-bacterial spectrum. It is highly potent against *Enterobacteriacae, Pseudomonas spp, Acinetobacter spp, H. influenzae* and anaerobic bacteria, with a fairly good potency against gram positive cocci [8, 14]. Its known action against resistant organisms has stimulated its use for treatment of serious hospital acquired infections [5, 14, 17].

In this study, meropenem showed efficacy as first choice treatment for respirator-associated and/or aspiration nosocomial pneumonia in the ICU, with 76% clinical improvement (48% cure, and 28% improvement). Mortality was 12% at the end of therapy and 24% after 4 to 6 weeks of follow-up. Our mortality rates were low compared to other studies [2, 6, 11, 13], especially when considering the high incidence of immunosuppression in our group.

Meropenem was shown to be safe, despite the high incidence of organ failure in this group. Adverse events were observed in 11 patients (44%), but only 5 patients presented severe adverse events (20%), none of them related to meropenem. Only 3 patients presented adverse events possibly related to meropenem (skin rash, seizure, and gastritis).

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