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Meropenem versus Cefuroxime plus Gentamicin for Treatment of Serious Infections in Elderly Patients

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In this multicenter study, the efficacy of and tolerability for meropenem were compared with those for the combination of cefuroxime-gentamicin (±metronidazole) for the treatment of serious bacterial infections in patients ≥65 years of age. A total of 79 patients were randomized; thirty-nine received meropenem (1 g/8 h), and 40 received cefuroxime (1.5 g/8 h) plus gentamicin (4 mg/kg of body weight daily) for 5 to 10 days. Metronidazole (500 mg/6 h) could be added to the cefuroxime-gentamicin regimen for the treatment of intra-abdominal infections ($n = 10$). Seventy patients were evaluable for clinical efficacy; the primary diagnoses were as follows: pneumonia in 41 patients (20 treated with meropenem, 21 treated with cefuroxime-gentamicin), intra-abdominal infection in 10 patients (7 meropenem, 3 cefuroxime-gentamicin-metronidazole), urinary tract infection (UTI) in 11 patients (6 meropenem, 5 cefuroxime-gentamicin), sepsis syndrome in 7 patients (4 meropenem, 3 cefuroxime-gentamicin), and "other" in 1 patient (cefuroxime-gentamicin). The pathogens isolated from 18 patients with bacteremia were as follows: *Staphylococcus* spp. ($n = 2$), *Streptococcus* spp. ($n = 2$), members of the family *Enterobacteriaceae* ($n = 11$), and *Bacteroides* spp. ($n = 3$). A satisfactory clinical response at the end of therapy was achieved in 26 of 37 (70%) and 24 of 33 (73%) evaluable patients treated with meropenem and combination therapy, respectively. Clinical success was achieved in 23 of 31 (74%) and 21 of 28 (75%) evaluable patients with infections other than UTIs, respectively. A satisfactory microbiological response occurred in 15 of 22 (68%) patients in the meropenem group compared with 12 of 19 (63%) treated with combination therapy. Renal failure occurred during therapy in 2 of 39 (5%) meropenem recipients compared with 5 of 40 (13%) of those treated with combination therapy. The findings in this small study indicate that meropenem is as efficacious for and as well tolerated by elderly patients as the combination of cefuroxime-gentamicin (±metronidazole).

In 1992, 6.2% of the global population was >65 years of age; this proportion is projected to expand to 20% by the year 2050 (8). The elderly are at increased risk for serious infection that may result in death, for a variety of reasons.

The diagnosis of infection in elderly patients may be difficult due to the presence of fewer clinical signs and symptoms and the problems involved in microbiological confirmation (8). Therefore, empirical antibiotic therapy is often necessary, and since the range of pathogens implicated in infections in elderly patients is more diverse than that in younger patients, a broad-spectrum antimicrobial regimen is often required. The treatment of infections in elderly patients is potentially complicated by alterations in the pharmacokinetic handling of antibiotics in these patients, and this group may be subject to an increased risk of toxicity caused by some antibiotics (8).

Meropenem is a newer carbapenem which appears to have several advantages over imipenem. Meropenem is relatively stable to DHP-I (2, 26) and, consequently, does not have to be administered with a DHP-I such as cilastatin. Both carbapenems have a uniquely broad antimicrobial spectrum which covers most clinically important gram-negative and gram-positive aerobic and anaerobic cocci and bacilli. Meropenem is more active than imipenem against *Enterobacteriaceae* and *Pseudomonas aeruginosa* but slightly less active against certain gram-positive cocci (e.g., staphylococci) (9). The only bacterial species that are normally resistant to the carbapenems are *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Corynebacterium jeikeium*, *Enterococcus faecium*, certain *Enterococcus* spp., and methicillin-resistant *Staphylococcus aureus*. Carbapenems are highly resistant to hydrolysis by almost all β-lactamases, including the mutant extended-spectrum β-lactamases produced by certain members of the family *Enterobacteriaceae*, e.g., *Klebsiella pneumoniae* (9).

Meropenem is well tolerated in the elderly population (27), but to the best of our knowledge only one European multicenter comparative study with meropenem has been performed. The study included elderly (>65 years) and nonelderly (<65 years) patients (22). Our study was designed to evaluate the efficacy of and tolerability for meropenem compared to those for a standard regimen in the Netherlands, cefuroxime plus

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gentamicin (with metronidazole if anaerobic pathogens were suspected) for the treatment of serious bacterial infections in patients ≥65 years of age.

MATERIALS AND METHODS

Patients. This nonblinded, randomized, parallel-group study was conducted in five hospitals in The Netherlands. Patients were eligible to participate in the study if they were ≥65 years of age, able to provide informed consent, and had one or more (proven or suspected) of the following serious bacterial infections: sepsis syndrome, intra-abdominal infection, lower respiratory tract infection (LRTI), complicated urinary tract infection (UTI) (3), and/or bacteremia. Patients with known hypersensitivity to β-lactam antibiotics were excluded, as were those with hepatic impairment (three times the upper reference limit of liver transaminases for each hospital), hepatic failure or hepatic coma, a granulocyte count of ≤500 cells/mm^3, cystic fibrosis, or a life expectancy of <48 hours. Patients who had previously participated in the trial or received another investigational drug or antibiotic within 30 days or 3 days prior to randomization, respectively (unless the organism was resistant), were not eligible to participate in the study.

Classification of infections. Nosocomial infections were defined according to the criteria of the U.S. Centers for Disease Control (10). Intra-abdominal infection was defined as a suspected or proven complicated infection derived from the gastrointestinal or reproductive tract, with signs and symptoms of fever (>38.3°C), leukocytosis, abdominal wall rigidity, and/or ileus. The infectious process had to extend beyond the site of origin, causing peritonitis or abscess formation (such as perforation, acute cholangitis, and periappendicular abscess). Pneumonia or LRTI was defined according to signs and symptoms such as chest pain, cough, and/or auscultatory findings (rales and/or evidence of pulmonary consolidation) with or without fever (>38.3°C) or leukocytosis and radiographic or other laboratory evidence supporting the diagnosis. Sputum was cultured if a Gram stain showed ≥25 leukocytes and ≤10 epithelial cells per high-power field. UTIs were defined as pyelonephritis or as a complicated UTI in the presence of an indwelling catheter or the use of intermittent catheterization, >100 ml of residual urine after voiding, obstructive uropathy due to bladder outlet obstruction or a calculus, vesicoureteral reflux or urologic abnormalities, azotemia due to intrinsic renal disease or occurring after renal transplantation. Patients with a complicated UTI were included only when signs and symptoms of a systemic infection occurred.

Sepsis syndrome criteria obtained at time of entry. The diagnosis of sepsis syndrome was based on the definition of Bone et al. (5), i.e., clinical evidence of infection plus the presence of fever or hypothermia (rectal temperature of >38.3°C or <35.6°C), tachypnea (>20 spontaneous breaths/min), tachycardia (>90 beats/min), and at least one of the following manifestations of inadequate organ perfusion or function: oliguria (<30 ml/h), hypoxemia (arterial oxygen pressure of <75 mm Hg while room air was being breathed), elevated plasma lactate, and/or mental alteration compared to baseline.

Treatment. Eligible patients were randomly assigned (in blocks of four) to a study group by means of consecutive sealed envelopes. Meropenem (Zeneca Farma, Ridderkerk, The Netherlands) was administered at a dosage of 1 g (dissolved in 20 ml of sterile water–80 ml of sterile isotonic saline) every 8 h; in cases of renal impairment, the dosages were as follows: for a creatinine clearance rate of 26 to 50 ml/min, 1 g twice a day (BID); for a rate of 10 to 25 ml/min, 0.5 g BID; for a rate of <10 ml/min, 0.5 g once daily. Cefuroxime (Glaxo Wellcome, Zeist, The Netherlands) was given at a dosage of 1.5 g (dissolved in 100 ml of sterile isotonic saline) every 8 h, in cases of renal impairment, the dosages were as follows: for a creatinine clearance rate of 10 to 50 ml/min, 1.5 g BID and for a rate of <10 ml/min, 1.5 g once daily. Gentamicin (Schering-Plough, Amstelveen, The Netherlands) was administered at a dosage of 4 mg/kg of body weight (dissolved in 100 ml of sterile isotonic saline) once daily or in two or three divided doses; in cases of renal impairment, the dosages were as follows: for a creatinine clearance rate of 50 to 70 ml/min, 1.8 mg/kg once daily; for a rate of 10 to 50 ml/min, 1.5 mg/kg once daily; and for a rate of <10 ml/min, 1.5 mg/kg every 2 days. Metronidazole (Rhône-Poulenc Rorer, Amsterdam, The Netherlands) was given at a dosage of 0.5 g (dissolved in 100 ml of sterile isotonic saline) every 6 h. All drugs were administered intravenously over 20 to 30 min, with a controlled delivery system; in cases of renal impairment, the dosages were as follows: for a creatinine clearance rate of 10 to 50 ml/min, 0.5 g three times a day and for a rate of <10 ml/min, 0.5 g BID. The duration of treatment depended on the clinical and bacteriological response, but a duration of 5 to 10 days (maximum 28 days) was recommended.

Assessment. (i) Clinical. At the time of entry into the study, a medical history was taken and each patient was examined for signs and symptoms of infection. The pretreatment severity of the infection was assessed with the APACHE II scoring system (16). In addition, a chest X-ray was performed in patients with suspected LRTI. Hematological tests (hemoglobin, hematocrit, total leukocyte count with differentiation, platelet count) and serum biochemistry tests (aspartate aminotransferase, alanine aminotransferase, albumin, alkaline phosphatase, bilirubin, and creatinine) were also performed. All procedures were performed once a week, at the end of treatment, and at other times when necessary. Renal failure was defined as an increase in serum creatinine of ≥40 μmol/liter when the baseline value was <300 μmol/liter and an increase of ≥80 μmol/liter when the baseline value was ≥300 μmol/liter (13). A follow-up clinical examination was performed 4 to 6 weeks after the end of therapy.

The clinical response was classified as satisfactory (all signs and symptoms relevant to the infection were resolved or improved at the end of treatment [non-UTI, directly after treatment; UTI, 5 to 9 days posttherapy], and no new symptoms were present at posttreatment follow-up [non-UTI, 2 to 4 weeks; UTI, 4 to 6 weeks]), unsatisfactory (persistence or worsening of clinical signs or symptoms relevant to the pretreatment infection or a need for an addition to or a change in the antimicrobial regimen), or indeterminable (no follow-up evaluation of clinical signs and symptoms). All patients were monitored for clinical, biochemical, and hematological adverse events. All adverse events were recorded.

(ii) Bacteriological. At least two blood specimens for cultures (both aerobic and anaerobic) were drawn when each subject entered the study. Also, urine samples were collected and, when possible, specimens from the site of infection were obtained for culture. If prior antimicrobial therapy had been administered, samples were taken after the previous antibacterials were stopped and before the therapy in the present study was started. Repeat cultures were taken from the same relevant sites from all patients except those with UTIs during and preferably immediately posttreatment. For patients with UTIs, a urine specimen was cultured before therapy, after 48 to 72 h, 5 to 9 days posttherapy, and 4 to 6 weeks after the end of therapy to identify relapses and superinfections. A blood culture set consisted of two bottles, Bactec (Becton Dickinson) and BacT Alert (Organon Technika, Oss, The Netherlands); one was aerobic, and the other was anaerobic. Each bottle was filled with 10 ml of blood. All procedures were followed in accordance with the manufacturer's recommendations, and isolates were identified by standard methods. Primary bacteremia was defined as isolation of a pathogen from the circulating blood without a known site of infection. Contamination was defined as isolation of a common (skin) contaminant (e.g., *Bacillus* spp., coagulase-negative staphylococci, and *Corynebacterium* spp.) from one of at least two blood cultures (10).

Antimicrobial susceptibility testing of each study antibiotic was conducted for all pathogens obtained from the site of infection or from blood. Susceptibility testing was performed by determination of the MIC, by E-test, or by both methods with the standard methods of the National Committee for Clinical Laboratory Standards (24, 25). Respective MIC breakpoints for susceptibilities to meropenem, cefuroxime, gentamicin, and metronidazole were ≤4, ≤4, ≤2, and ≤2 mg/liter. The corresponding MIC breakpoints for resistance were >16, >16, >8, and >4 mg/liter, respectively.

Patients were microbiologically evaluable if pretreatment culture specimens were positive. The microbiological response was classified as eradication (all cultures obtained after the completion of therapy and at posttreatment were negative [<10^3 CFU/ml for patients with UTIs], or no material for culture was available due to diminished sputum production, lack of purulent material, or healing of the infected site), persistence or relapse (the pretherapy causative pathogen was present during treatment or reappeared after the termination of treatment [≥10^4 CFU/ml for patients with UTIs]), superinfection or reinfection (a new pathogen plus symptoms appeared during or after therapy, respectively), colonization (a pathogenic microorganism was present without any symptoms of infection), or undetermined. When the pretreatment culture was found to be negative, the infection was considered only clinically documented. Patients were considered microbiologically unevaluable when there was a viral or fungal infection, protocol was violated, they died within the first 48 h, a resistant microorganism was suspected, and/or in cases of misdiagnosis.

Statistical analysis. A power calculation was performed after recruitment; the expected midpoint of a 95% confidence interval (CI) for a response rate of approximately 70% is 20%. The primary endpoint was the clinical response to therapy at the end of treatment. The secondary endpoints were bacteriological response and tolerability. Statistical analyses of dichotomous variables were done by the two-sided Fisher exact test at a 5% level of significance. Standard approximate 95% CIs for differences in proportions are given. Results were analyzed by the intention-to-treat principle as well as by evaluability.

RESULTS

Patients. During an 11-month period, a total of 79 patients participated the study (University Hospital Utrecht, Utrecht, The Netherlands, $n = 20$; St. Antonius Hospital, Nieuwegein, The Netherlands, $n = 9$; Elkerliek Hospital, Helmond, The Netherlands, $n = 7$; St. Elisabeth Hospital, Tilburg, The Netherlands, $n = 19$; and Sophia Hospital, Zwolle, The Netherlands $n = 24$). Of these patients, 39 were randomized to receive meropenem and 40 were randomized to receive cefuroxime-gentamicin. Gentamicin was administered once daily, BID, or in three divided doses to 30, 7, and 2 of the latter patients, respectively (1 patient did not receive gentamicin due to severe preexisting renal failure). Metronidazole was administered to 15 patients receiving the combination regimen. The mean (range)

TABLE 1. Demographic characteristics of evaluable patients

Characteristic	Meropenem	Cefuroxime-gentamicin (±metronidazole)
No. of patients	37	33
Sex (no. of males/no. of females)	20/17	25/8
Mean age, yr (range)	76 (67–89)	76 (65–91)
Mean treatment duration, days (range)	7.5 (3–21)	7.4 (3–17)
Mean APACHE II score (range)	18 (10–29)	20 (6–41)
No. of patients with indicated underlying disease[a]		
Bronchopulmonary	19	12
Cardiovascular	48	45
Diabetes mellitus	4	6
Gastrointestinal	27	18
Genitourinary	12	13
Immunocompromised	5	3
Neurological	8	15
Other	19	22

[a] Patients may have had more than one underlying disease.

duration of treatment was 7.5 days (3 to 21 days) in the meropenem group and 7.4 days (3 to 17 days) in the combination arm (Table 1). The means of the total numbers of doses of meropenem, cefuroxime, gentamicin, and metronidazole administered were 19, 19, 5, and 26, respectively.

Seventy patients (37 receiving meropenem, 33 receiving combination therapy) were evaluable for clinical efficacy. Nine were not evaluable for the following reasons: death ($n = 6$), misdiagnosis ($n = 1$), suspected resistant microorganism ($n = 1$), and <48 h of therapy ($n = 1$). Forty-one patients (22 meropenem, 19 combination therapy) were evaluable for microbiological efficacy.

The evaluable patients in the two treatment groups were similar with respect to sex distribution, mean age, treatment duration, and APACHE II scores (Table 1). However, there were more patients with underlying gastrointestinal and bronchopulmonary diseases in the meropenem group and more with neurological diseases in the combination group. Dosage adjustments for patients with impaired renal function were necessary in 24 (30%) patients, 18 who received meropenem and 6 who received combination therapy.

The numbers of clinically documented infections were similar in the meropenem and combination therapy groups (33 versus 37%, respectively). Pneumonia was the most common infection in both groups, followed by intra-abdominal infection, UTI, and sepsis syndrome (Table 2).

Clinical efficacy. On an intention-to-treat basis, the clinical response at the end of therapy was satisfactory in 69% (27 of 39) of patients treated with meropenem and in 63% (25 of 40; $P = 0.64$; 95% CI, −14 to 23%) of those treated with cefuroxime-gentamicin (±metronidazol). All patients that died were classified as failures. The clinical response in evaluable patients at the end of therapy was satisfactory in 26 of 37 (70%) patients treated with meropenem and 24 of 33 (73%; $P = 1.00$; 95% CI, −24 to 19%) of those treated with cefuroxime-gentamicin (±metronidazole) (Table 2) ($P = 1.00$). In patients with infections other than UTIs, a satisfactory response occurred in 23 of 31 (74%) of meropenem patients compared with 21 of 28 (75%) of combination therapy patients.

An unsatisfactory clinical response occurred in seven patients in each group. There were no important differences in sex, age, site of infection, treatment duration, or APACHE II scores between the meropenem- and cefuroxime-gentamicin-treated patients in whom treatment failed (Table 3). In the meropenem group, one patient died during treatment, three patients were changed to another antibiotic regimen, and three patients received no subsequent antibiotics. In the combination therapy group, five patients were changed to another antibiotic regimen, one patient was cured without subsequent antibiotics, and the remaining patient died after 3 days without subsequent antibiotics.

Relapse occurred in one patient with UTI in each group. The organisms responsible for the relapse in the meropenem-treated patient were *Escherichia coli* and *Enterococcus* spp. (both sensitive to meropenem; MIC, 0.5 mg/liter). The organism responsible for the relapse in the patient treated with combination therapy (cefuroxime MIC, 2 mg/liter; gentamicin MIC, 4 mg/liter) was *E. coli*. Reinfection also occurred in one meropenem-treated patient with a UTI (not associated with a urinary catheter) caused by *E. coli* (meropenem MIC, 0.32 mg/liter).

A satisfactory clinical response at follow-up (for non-UTI patients, 2 to 4 weeks; for UTI patients, 4 to 6 weeks) was obtained in 29 of 37 (78%) evaluable patients treated with meropenem compared with 64% (21 of 33; $P = 0.20$; 95% CI, −6 to 36%) of those who received combination therapy. In the meropenem group, one failure and one relapse (pulmonary infection with *Pseudomonas aeruginosa*) occurred, and three patients were unevaluable at the end of follow-up. In the combination therapy group, three patients had a relapse (two pulmonary infections, one caused by *Enterobacter aerogenes* and one by *Morganella morganii*, and an intra-abdominal infection), and two patients were unevaluable.

TABLE 2. Outcome in clinically documented infections in evaluable patients

Type of infection	No. of patients (%) treated with[a]:			
	Meropenem		Cefuroxime-gentamicin (±metronidazole)	
	Total	Satisfactory outcome	Total	Satisfactory outcome
Primary				
Urinary tract	6	3 (50)	5	3 (60)
Intra-abdominal	7	4 (57)	3	2 (67)
Pneumonia[c]	20	17 (85)	21	16 (76)
Sepsis syndrome alone	3	2 (50)	1	
Sepsis syndrome with other	1		2	2 (50)
Other[d]	1		3[e]	
Bacteriologically documented	22 (60)		19 (58)	
Polymicrobial	11 (30)		7 (21)	
Total	37	26 (70)	33	24 (73)[b]

[a] No significant difference in clinical outcome between the groups ($P = 1.00$; 95% CI, −24 to 19%).

[b] One patient in the cefuroxime-gentamicin (metronidazole) group with another infection also improved.

[c] No significant difference in clinical outcome between the groups ($P = 1.00$; 95% CI, −26 to 21%).

[d] Some patients had more than one type of infection.

[e] A patient with decubitus was treated with cefuroxime-gentamicin and metronidazole for 20 days.

TABLE 3. Characteristics of patients in whom clinical failure occurred

Treatment group	Age (yr)	Sex[a]	Type of infection	Pathogen	Susceptibility[b]	Treatment duration (days)	APACHE II score	Sepsis syndrome	Follow-up
Meropenem	82	F	Sepsis syndrome	None		5	13	Yes	Changed to cefuroxime and gentamicin
	69	M	Intra-abdominal	*Escherichia coli*, *Streptococcus oralis*	S	3	18	Yes	Died after ruptured infected aorta bypass
	74	F	Pneumonia	None	ND	8	12	No	No subsequent antibiotics
	78	F	Intra-abdominal	*Klebsiella oxytoca*, *Escherichia coli*, *Bacteroides* spp., *Staphylococcus epidermidis*	S	4	14	No	Changed to piperacillin-tazobactam
	74	M	Sepsis syndrome	*Staphylococcus aureus*	S	8	20	Yes	Changed to meropenem and vancomycin
	69	M	Pneumonia	None	NA	6	10	No	No subsequent antibiotics
	83	M	Pneumonia	*Streptococcus pneumoniae*	S	0	16	No	No subsequent antibiotics
Cefuroxime-gentamicin (±metronidazole)	68	M	Intra-abdominal	*Klebsiella pneumonia*	S	17	19	No	Changed to cotrimoxazole
			Pneumonia	*Pseudomonas aeruginosa*	R				
	78	M	Sepsis syndrome	*Enterococcus* spp.	R	3	21	Yes	No subsequent antibiotics
	77	M	Sepsis syndrome	*Serratia* spp.	I	3	22	Yes	Changed to cotrimoxazole
			Pneumonia	*Haemophilus influenzae*	S				
	76	F	Pneumonia	*Escherichia coli* *Streptococcus haemolyticus*	S ND	6	25	No	No subsequent antibiotics Died after asystole
	71	M	Pneumonia	None	NA	4	14	No	Changed to erythromycin
	73	M	Pneumonia	*Enterobacter* spp.	I	3	23	No	Changed to imipenem-cilastatin
	83	M	Pneumonia	*Enterobacter cloacae*	S	7	19	No	Changed to piperacillin, tobramycin, and later to ceftazidime
				Pseudomonas aeruginosa	R				

[a] F, female.
[b] S, susceptible; ND, no data available; NA, not applicable; R, resistant; I, intermediate.

Bacteriological efficacy. Microbiologically documented infections were present in 41 of 70 (59%) clinically evaluable patients (Table 4). The majority of infections were caused by gram-negative organisms ($n = 57$ [26 patients receiving meropenem, 31 patients receiving combination therapy]). There were 26 gram-positive infections (19 meropenem, 7 combination therapy) and 6 anaerobic infections (4 meropenem, 2 combination therapy) (Table 4). There were more gram-positive infections in the meropenem group and more gram-negative infections in the combination therapy group.

The predominant pathogens were *Enterobacteriaceae* ($n = 54$) (*Enterobacter* spp., $n = 5$; *E. coli*, $n = 30$; *Proteus* spp., $n = 5$; *K. pneumoniae*, $n = 6$; *Klebsiella oxytoca*, $n = 2$; *Serratia* spp., $n = 2$; *Citrobacter* spp., $n = 1$; *Morganella* spp., $n = 2$; and *Providencia* spp., $n = 1$), *Staphylococcus aureus* ($n = 8$), *Streptococcus* spp. ($n = 5$), *Streptococcus pneumoniae* ($n = 4$), *Pseudomonas* spp. ($n = 2$), anaerobes ($n = 6$) (*Bacteroides* spp., $n = 4$; *Clostridium* spp., $n = 2$), and other gram-positive ($n = 9$) and gram-negative bacteria ($n = 1$). A single pathogen was found in 23 patients (11 receiving meropenem, 12 receiving combination therapy), whereas polymicrobial infections were documented in 18 patients (11 receiving meropenem and 7 receiving combination therapy). Bacteremia was found in 18 of 79 patients (23%) and was caused by the following microorganisms: *E. coli* ($n = 6$), *Bacteroides* spp. ($n = 3$), *K. pneumoniae* ($n = 2$), *M. morganii* ($n = 2$), *S. aureus* ($n = 2$), *Serratia* spp. ($n = 1$), *Streptococcus* spp. ($n = 1$), and *S. pneumoniae* ($n = 1$).

No significant difference in the microbiological success rate was seen between patients treated with meropenem and those treated with combination therapy (15 of 22 [68%] versus 12 of 19 [63%]; $P = 0.75$; 95% CI, −24 to 34%) (Table 4). Microbiological success was achieved in 79% (15 of 19) of patients with non-UTI infections in the meropenem group compared with 71% (12 of 17; $P = 0.71$; 95% CI, −20 to 37%) in the combination therapy group (Table 4). For patients with pneumonia, microbiological success was achieved in 83% (10 of 12 receiving meropenem) and 69% (9 of 13 receiving combination therapy), respectively (Table 4).

In the meropenem group, all pathogens cultured at the time of entry into the study and during the study were susceptible to meropenem (the E-test results for *Enterobacteriaceae*, *S. au-*

TABLE 4. Outcome in microbiologically documented infections in evaluable patients

Type of infection	No. of patients (%) treated with[a]:			
	Meropenem		Cefuroxime-gentamicin (±metronidazole)	
	Treatment	Eradication	Treatment	Eradication
Bacteriologically documented	22 (60)		19 (58)	
With bacterium-positive blood culture	9 (24)		9 (27)	
Pneumonia[b]	12	10 (83)	13	1 (69)
Gram-positive				
Staphylococcus aureus	6 [1][c]		2 [1]	
Streptococcus pneumoniae	3		1 [1]	
Streptococcus spp.	2 [1]		3	
Other	8		1	
Gram-negative				
Enterobacteriaceae	24 [5]		30 [6]	
Pseudomonas spp.	2		0	
Other		1		
Anaerobic	4 [2][d]		2 [1][e]	
Total	37	15/22 (68)	33	12/19 (63)

[a] No significant difference in bacteriological outcome between the groups (P = 0.75; 95% CI, −24 to 34%).
[b] No significant difference in bacteriological outcome between the groups.
[c] Figures in brackets denote numbers of bacterium-positive blood cultures.
[d] Blood cultures positive for *Bacteroides* spp.
[e] Blood cultures positive for *Bacteroides fragilis.*

reus, *Streptococcus* spp., and *Pseudomonas* spp. were 0.36, 0.15, 0.82, and 1.0, respectively). In the combination therapy group, two intermediate-susceptible pathogens to cefuroxime (*Serratia* spp. and *Enterobacter cloacae*; MICs, undetermined and 8 mg/liter, respectively) were cultured at the time of entry into the study, whereas during the study, four resistant pathogens (*P. aeruginosa* [n = 2]), *Enterococcus* spp. [n = 1], and *S. maltophilia* [n = 1]; MICs, 256, 256, and 256 mg/liter) were cultured.

Tolerability. All patients were included in the evaluation of tolerability. Adverse events were reported in 19 of 39 (48.7%) meropenem-treated patients compared to 18 of 40 (45.0%; P = 0.82; 95% CI, −18 to 26%) patients treated with combination therapy. The most common adverse events were impaired liver function (meropenem, n = 9; combination therapy, n = 5), diarrhea (meropenem, n = 4; combination therapy, n = 1), and renal failure (meropenem, n = 2; combination therapy, n = 5; P = 0.43; 95% CI, −20 to 5%). All adverse events, except renal failure with electrolyte disturbance, were mild. Three patients (two receiving meropenem, one receiving combination therapy) required hemodialysis for a short period.

Mortality was 8% (3 of 39) in the meropenem group versus 10% (4 of 40; P = 1.00; 95% CI, −15 to 10%) in the combination therapy group. All deaths (except one in the meropenem group) occurred within 48 h after the start of treatment. In no case was death attributable to the medication used in the study. In the meropenem group, two patients died of septic shock and one died as the result of a ruptured infected aorta prosthesis. Of the four patients in the combination therapy group who died, one died of ventricular fibrillation, one died of cerebral edema after neurosurgery, one died of septic shock, and one died of infection.

DISCUSSION

In elderly patients with serious infections, a delay in the selection of antibiotics and/or the incorrect choice of antibiotics are likely to have a significant impact on treatment outcome. Combination antibiotic therapy is widely used but, compared to monotherapy, may require more personnel time and may increase treatment costs, the risk of toxicity, and patient inconvenience (4, 13). Effective empirical therapy with a single-drug regimen would help to overcome these problems.

The results of this small multicenter study indicate that meropenem (1 g three times per day) is an effective empirical monotherapy for infections in severely ill, elderly patients with or without bacteremia. The patient population was characterized by relatively high mean APACHE II scores and the presence of underlying diseases. There was no significant difference between the rates of satisfactory clinical response achieved with meropenem and those achieved with cefuroxime-gentamicin (±metronidazole), a standard treatment regimen in The Netherlands (70 versus 73%). Another randomized study reported a higher overall rate of clinical success with meropenem (93 versus 79% with ceftazidime-amikacin) in patients with serious bacterial infections (22). Currently, a randomized study with a low dosage of meropenem (500 mg three times per day) for serious infections is under way.

A wide range of pathogens were isolated from patients in this study. The observed rates of satisfactory microbiological response with meropenem are lower than those from certain other trials with meropenem in patients with community-acquired LRTIs (22, 29), intra-abdominal infections (6, 11, 14), complicated UTI (7), and septicemia (30). A lower rate of microbiological eradication would be expected in our study because it involved only elderly patients, in whom bacterial eradication may be compromised by age-related immune deficiencies. The risk of resistance emerging during therapy is always a concern when empirical broad-spectrum monotherapy is used. However, there was no evidence of the development of meropenem resistance in this study within the follow-up period, but the size of the study does not allow conclusive evidence for single pathogens or for clinical conditions other than pneumonia.

Both drug regimens employed were well tolerated. Most adverse events reported were mild (e.g., diarrhea, phlebitis, and elevated liver transaminases) and occurred with similar frequency in both groups. We observed a higher incidence of diarrhea in the meropenem group (10%) than that reported from the international clinical trials program with meropenem (4.3% overall, 1.9% drug related) (27). However, since the latter analysis (which involved a total of 3,220 patient exposures) indicated that the adverse event profile of meropenem in elderly patients does not differ from that in younger patients, this difference may simply be due to the relatively small number of patients in our trial.

Since renal function declines in the elderly, the pharmacokinetics of a drug in the presence of renal impairment is an important concern for elderly patients. Meropenem is primarily excreted by the kidneys, and the elimination half-life in healthy young volunteers is approximately 1 h (2). The elimination half-life is slightly prolonged in the elderly; a value of 1.27 h was observed in one study with healthy elderly men (18, 26). Therefore, dosage adjustments, made according to creatinine clearance, may be required in elderly patients (21).

The development of renal failure during therapy was reported in two patients (5%) treated with meropenem in the present trial and in 5 (15%) of those treated with combination therapy. Data from both animal and clinical studies have shown that meropenem is well tolerated by the kidneys (27, 31). An overall incidence of 0 to 25% for nephrotoxicity caused by aminoglycosides is reported in the literature (13, 19, 20, 23, 28), and the risk is increased in patients with renal impairment. In recent years, once-daily administration of aminoglycosides has been shown to be at least as effective as multiple daily administration in the treatment of certain types of infections (1, 12, 15). Once-daily administration of gentamicin was associated with a lower incidence of nephrotoxicity in two studies (1, 12) but not in another meta-analysis (23). In elderly patients, however, pharmacokinetic monitoring may be better (17). Thus, any drugs for elderly patients must be selected carefully and may require monitoring. The routine use of aminoglycosides in elderly patients should be avoided when possible (8, 17). In The Netherlands, a 1-day dosage of meropenem costs approximately $120 versus $79 in a control group, not including costs for monitoring gentamicin levels in the blood and for extra personnel for the administration of antibiotics.

In conclusion, in this small study, meropenem monotherapy (1 g every 8 h) was as efficacious as combination therapy for the empirical treatment of serious infections in the elderly, producing high rates of clinical and microbiological success without serious adverse events. Meropenem was well tolerated and offers greater flexibility of administration than cefuroxime plus gentamicin.

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