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Empirical monotherapy with meropenem in serious bacterial infections in children

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The efficacy and safety profile of meropenem were analyzed according to data collected from hospitalized pediatric patients aged 4 days to 20 years who had serious bacterial infections and were treated in a major teaching hospital in Taipei. Of the 53 patients enrolled, 47 were analyzed for clinical efficacy and 53 for safety. The satisfactory clinical response rate was 57% in lower respiratory tract infection, 58% in septicemia, 100% in complicated urinary tract infection, osteomyelitis, and central nervous system infection, 83% in skin and soft tissue infection, and 93% in intra-abdominal infection. Eleven (21%) patients experienced adverse events related to meropenem. The most commonly observed adverse reactions were elevated hepatic enzymes (7.5%), increased alkaline phosphatase (3.8%), and thrombocytosis (3.8%). There was no meropenem-related seizure, withdrawal, or death. The results of this study suggested that meropenem is well tolerated even in young infants, and is effective in treating serious childhood bacterial infection. However, this study also identified a proportion of hospitalized pediatric patients with isolates that were resistant to meropenem. The trends in meropenem resistance among nosocomially acquired bacteria should be monitored closely.

Key words: Adverse reaction, children, efficacy, meropenem

The emergence of multidrug-resistant pathogens has led to increased use of alternative broad-spectrum antibiotics. Carbapenem possesses excellent activity against most gram-positive and -negative bacteria. This broad spectrum of activity makes carbapenem appropriate for empirical therapy in the treatment of serious infections.

Two carbapenems, imipenem and meropenem, are currently available. In general, imipenem and meropenem share a similar spectrum of antibacterial activity. However, the use of imipenem is faced with the concern of gastrointestinal toxicity and neurotoxicity [1,2]. In addition, imipenem has to be co-administered with a dehydropeptidase inhibitor (cilastatin) to avoid extensive renal metabolism and nephrotoxicity [3]. Meropenem is the second carbapenem to become available, and has first come to clinical use in 1994. It was investigated extensively in clinical trials during the early 1990s [4-8]. A review of the safety profile of meropenem based on 3125 patients found that it was well tolerated without significant adverse involvement of the central nervous system (CNS) and gastrointestinal tract [9].

Meropenem was introduced into clinical practice in Taiwan in 1999, there has not been sufficient data to evaluate its efficacy and safety profile in Taiwan children. This open, prospective study of hospitalized children with serious bacterial infection including neonates and young infants evaluated the efficacy and tolerability of meropenem.

Materials and Methods

Study design and population

From February through March 2000, patients aged 4 days to 20 years with severe infections who were admitted to the pediatric ward of the National Taiwan University Hospital were evaluated to determine their eligibility for enrollment. The exclusion criteria were as follows: (1) a history of allergic reaction to beta-lactam antibiotics or immediate hypersensitivity to meropenem; (2) known hepatic failure or coma; (3) treatment with antibiotics in the past 3 days before enrollment (unless the bacteria was resistant or shown to be still present); (4) renal failure; and (5) a history of seizure disorder. A total of 53 patients were enrolled in

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this 13-month period.

The underlying disease of the patient at the beginning of meropenem therapy was classified as rapidly fatal, ultimately fatal, or nonfatal [10]. Patients who had refractory leukemia with blast crisis were classified as having rapidly fatal disease. The classification of patients as having ultimately fatal disease was based on the severity of the underlying illness rather than the specific diagnosis. These patients had disease that was estimated to become fatal within 4 years; they included patients with severe aplastic anemia, biliary atresia with liver cirrhosis, and dilated cardiomyopathy with heart failure. Patients with gastrointestinal tract anomaly, congenital heart disease, prematurity with chronic lung disease, or urinary tract anomaly were classified as having nonfatal underlying disease.

The general condition of patients at study entry was classified as critical (condition rapidly deteriorating, with death in a short period of time not unlikely), poor (condition deteriorating, with death possible but not imminent), or fair (condition deteriorating but death not likely) [11].

Antibiotic therapy and microbiologic methods

Meropenem was administered by intravenous bolus injection over 5 min at a dose of 20 to 40 mg/kg every 8 h. The dose and frequency was adjusted based on the severity of infection and the status of renal function. The dosage of meropenem was 20 to 30 mg/kg every 12 h if the estimated creatinine clearance (CCr) was between 25 and 50 mL/min, and 20 to 30 mg/kg every 8 h for a CCr over 50 mL/min. A higher dosage (100-120 mg/kg/d, q8h) was administered to patients with CNS infection or underlying rapidly fatal disease who were in a critical condition. Kirby-Bauer disc sensitivity testing and determination of the minimal inhibitory concentration of meropenem were performed for all isolates. The susceptibilities were reported according to the National Committee for Clinical Laboratory Standards criteria [12].

Assessment and monitoring

The classification of infection and definition of secondary infection was as described in the literature [4]. Hematological and biochemical tests were performed before the initiation of meropenem therapy, 7 days after treatment, at least once weekly thereafter and as clinically warranted, and within 24 h of cessation of treatment. Abnormal values of laboratory tests were monitored until they returned to normal ranges. Patients were examined daily for clinical evidence of drug toxicity. Clinical follow-up examination was performed at least 14 days after stopping treatment.

Evaluation of responses

Patients were considered cured if all the following 3 criteria were met without a change in the regimen: (1) the body temperature was normal for at least 4 consecutive days; (2) the symptoms and signs of the infection had resolved; and (3) the primary infection had not recurred within 1 week after stopping therapy. If patients had initial improvement but developed secondary infection, the outcome of therapy was considered successful. Failure was defined as persistent fever after at least 72 h of empirical therapy, persistent isolation of pathogen, unchanged status or progression of primary infection, relapse of fever, breakthrough or persistent bacteremia, death from the primary infection, shock, acute respiratory distress syndrome (ARDS), multiple organ failure, and withdrawal of treatment because of drug toxicity. The bacteriological response was assessed at the end of therapy and during the follow-up period of 1 to 2 weeks. Bacteriological response was considered satisfactory if the primary pathogen was sensitive to meropenem and its presence had been

Table 1. Characteristics of patients who completed the meropenem regimen (n = 47)

Demographic data	No. of patients (%)
Male/female	30/17 (64/36)
Mean age, year (range)	2 (4 days-20 years)
Underlying disease excluding malignancy	31 (66)
Underlying malignancy	13 (27)
Acute leukemia	10 (21)
Solid tumor	1
Others	2
Rapidly or ultimately fatal disease	16 (34)
General condition	
Fair	17 (36)
Poor	21 (45)
Critical	9
Mean pretherapy duration of symptoms, day (range)	11 (1-47)
Neutropenia ($\leq$1000/mm^3)	12 (26)
At study entry	11 (23)
Persisted during meropenem use	7
Median duration, day (range)	22 (6-82)
Median ANC at entry (range)	0 (0-262)
Presence of shock at meropenem start	9
Previous antibiotics use	47 (100)

Abbreviation: ANC = absolute neutrophil count

eliminated or decreased. Responses were considered unsatisfactory if persistence or resistance of the primary pathogen to meropenem developed (failed response) or if superinfection developed.

Results

Patients

Treatment efficacy was assessed in all but 6 patients, 2 of whom had congenital heart disease with heart failure and died of cardiogenic shock; 2 had concurrent administration of other effective antibiotics; one died within 48 h after starting treatment; and one patient, a premature baby, had unstable vital signs unrelated to infection. Data of the remaining 47 patients can be evaluated and were included in the analysis.

Table 1 shows the characteristics of the 47 patients who completed the study regimen. The majority of these patients (44/47) had underlying disease, which included congenital heart disease (n = 10), prematurity with chronic lung disease (n = 3), intraventricular hemorrhage (n = 2), gastrointestinal tract malformation (n = 10), airway anomaly with tracheostomy (n = 2), ureter-pelvis junction obstruction (n = 1), biliary atresia with liver cirrhosis (n = 2), severe aplastic anemia (n = 2), acute lymphomatous leukemia (n = 3), acute myelocytic leukemia (n = 7), chronic granulomatous disease (n = 1), and rhabdomyosarcoma (n = 1). The underlying diseases were rapidly or ultimately fatal in 16 (34%) of the 47 cases, and two-thirds of patients were in a critical or poor condition at study entry.

Treatment and outcome of therapy

The median time to resolution of fever was 5 days, and the median duration of therapy was 19 days. Treatment was successful in 34 (72%) patients, including cure in 21 (44%) and initial improvement with secondary infection in 13 (28%) cases. Meropenem treatment failed in 13 (28%) of the 47 patients. The result of intention-to-treat analysis was similar. Treatment was successful in 70% (37/53) of patients and failed in 30% (16/53). Persistent fever was the primary reason of treatment failure in 12 patients. Of them, 3 patients had persistent or breakthrough bacteremia, 2 had harbored resistant pathogens, and 3 experienced progression of primary infection. Four patients developed septic shock, 3 of them had ARDS, and one had disseminated intravascular coagulation.

Clinical and bacteriological efficacy

Tables 2 and 3 show the clinical and bacteriological response to meropenem therapy for different infection site.

Twenty-one patients had hospital-acquired lower respiratory tract infection (LRTI), manifesting as interstitial pneumonia or bronchopneumonia. Seventeen (82%) of them can be evaluated bacteriologically. Infections were mostly caused by gram-negative organisms, and *Pseudomonas aeruginosa* was the leading isolated pathogen (35%, 6/17). A successful clinical response (cure or improvement) was observed in 57% of patients, and a satisfactory bacteriological response (elimination or decrease) rate of 53% was recorded.

Table 2. Clinical responses by infection site (n = 59)

Site of infection	No. of patients (%)	
	Cured/improved	Unchanged/worsened
Lower respiratory tract		
Community acquired (n = 1)	1	0
Hospital acquired (n = 21)	12 (57)	9 (43)
Septicemia		
Gram-positive (n = 3)	0	3
Gram-negative (n = 9)	7	2
Complicated UTI (n = 1)	1	0
Skin and soft tissue (n = 6)	5	1
CNS (n = 1)	1	0
Intraabdominal infection (n = 14)	13 (93)	1 (7)
Bone and joint (n = 1)	1	0
Unidentified (n = 2)	1	1
Total	42 (71)	17 (29)

Abbreviations: UTI = urinary tract infection; CNS= central nervous system
Note: some patients had multiple sites of infection

Table 3. Bacteriological response by site of infection (n = 49)

Site of infection	No. of isolates (%)		
	Eradicated	Relapse	Superinfection
Lower respiratory tract			
Community acquired	0	0	0
Hospital acquired	9 (53)	5 (29)	3 (18)
Septicemia			
Gram-positive	0	3	0
Gram-negative	5	3	1
Urinary tract	1	0	0
Skin and soft tissue	3	1	2
Central nervous system	1	0	0
Intra-abdominal	7	3	1
Bone and joint	1	0	0
Total	27 (55)	15 (31)	7 (14)

Note: some patients had multiple sites of infection

Only one case of community-acquired pneumonia with pleural effusion was included in this study. The culture showed no growth and the clinical response of the patient was good.

A total of 12 patients with septicemia completed the study regimen. The response was poor in all patients with gram-positive bacteremia, and was much better for those with gram-negative septicemia, with a favorable clinical response in 78% (7/9) of patients and a satisfactory bacteriological response in 56% of patients.

The intraabdominal area was the second most common site of infection, with a total of 14 (30%, 14/47) patients involved. Three patients had intra-abdominal infections without identified pathogens, and all of them had successful clinical responses. There were 3 patients with no bacteriological response, but 2 of them showed clinical improvement. Excellent clinical response was seen (93%, 13/14), with at least 64% of patients showed bacteriological response.

The number of patients with osteomyelitis, complicated urinary tract infection, and CNS infection was only one each, and all of these patients had excellent clinical and bacteriological response (100%).

There were 6 patients with skin and soft tissue infections. The majority of them (5/6, 83%) experienced clinical cure or improvement, and 50% had good bacteriological response.

Table 4 shows all of the isolated pathogens and their microbiologic responses to meropenem. Of the 49 available isolates, gram-negative aerobic bacteria accounted for the majority (36, 73%), followed by gram-positive bacteria (12, 25%) and anaerobic bacteria (1, 2%). Meropenem was effective in treating gram-negative infections, but was less active in gram-positive infections.

Mortality and secondary infection

The overall mortality rate was 15% (7/47), and the causes of death included progression of primary infection in one patient, refractory cancer with septic shock in 4, and other causes in 2. No death was considered to be related to meropenem usage.

Eighteen (38%) patients developed superinfection during meropenem therapy. Pneumonia and bacteremia were the two most commonly encountered problems.

Table 4. Bacteriological response to meropenem therapy stratified by pathogen

Microorganism	No. of susceptible isolates (%)
Gram-positive cocci (n = 12)	3 (33)
MRSA (n = 5)	0
Coagulase-negative staphylococci (n = 4)	2
Enterococcus faecalis (n = 3)	1
Gram-negative bacilli (n = 36)	24 (60)
Escherichia coli (n = 4)	4
Pseudomonas aeruginosa (n = 8)	7
Stenotrophomonas maltophilia (n = 4)	1
Serratia marcescens (n = 3)	1
Enterobacter cloacae (n = 7)	7
Klebsiella pneumoniae (n = 3)	3
Acinetobacter baumannii (n = 3)	0
Other gram-negative bacteria, n = 4)	1
Anaerobes	1
Bacteroides sp. (n = 1)	1

Abbreviation: MRSA = methicillin-resistant *Staphylococcus aureus*

Fungi were responsible for one-third of the superinfections.

Adverse events

A total of 53 patients entered this study and received meropenem. All cases were analyzed for adverse events. The clinical and laboratory adverse events associated with meropenem are listed in Table 5. Thirty-one (58%) of the 53 patients experienced at least one adverse event, and in 11 (21%) patients the adverse events were considered to be related to meropenem. There was no withdrawal of meropenem because of adverse effects. The incidence of adverse events was significantly higher in patients younger than 3 months than those older than 3 months (42% vs 11%; $p<0.05$).

Discussion

The advent of new broad-spectrum antibiotics such as carbapenem has offered the prospect of single agent therapy. In this study of empirical monotherapy with meropenem in children with serious bacterial infection, the treatment outcome was successful in 72% of patients. A satisfactory clinical response was achieved in 57% to 100% of patients according to the site of infection, and the favorable bacteriological response rate of all pathogens was 55%. About one-fifth of the patients developed adverse reactions that were considered to be due to meropenem use, and all of them were mild. These data, which were similar to those reported in other populations [4-8], indicated the high effectiveness and good safety profile of meropenem in severe childhood infection among Taiwanese.

While meropenem and imipenem are similar in many aspects, meropenem has been reported to induce less neurotoxicity and gastrointestinal toxicity [13,14]. This phenomenon was also observed in this series. The epileptogenic potential of β-lactam agents including imipenem can be attributed to the inhibition of receptor binding of β-aminobutyric acid [15]. In this study, 3 patients experienced seizures, but none of the seizures were considered to be related to meropenem, and all 3 patients had pre-existing CNS disorder (one each had ventriculitis, porencephaly, and Grade 3-4 IVH and hydrocephalus). Drug-related diarrhea was noted in only one of 12 patients with febrile neutropenia, and drug-related nausea or vomiting was not seen. Recent studies have shown that when meropenem was administered by standard infusion or intravenous bolus injection, a similar low incidence of nausea and vomiting was observed [16], which is unusual for imipenem-cilastatin (2.9%-7.7%) [17]. A prior review of the safety profile of meropenem in nearly 5000 patients reported that the adverse events experienced by more than 1% of exposure included increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), thrombocytosis, diarrhea, skin rash, nausea, vomiting, and injection site inflammation [18].

Table 5. Adverse events related to meropenem treatment (n = 53)

Adverse event	No. of cases (%)
Rash	1 (1.9)
Diarrhea	1 (1.9)
Thrombocytosis	2 (3.8)
Eosinophilia	1 (1.9)
AST elevation	4 (7.5)
ALT elevation	4 (7.5)
ALP elevation	2 (3.8)
LDH elevation	1 (1.9)
Bilirubin elevation	1 (1.9)

Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; LDH = lactate dehydrogenase

In this study, the meropenem-related clinical adverse events observed most frequently were diarrhea and rash; however, these occurred only in less than 2% of patient exposures. The most common laboratory adverse events were thrombocytosis and increased hepatic enzymes and ALP, but these elevations were clinically insignificant. Nevertheless, we observed a higher incidence (21%) of adverse reactions compared with previous studies (3.7%-16%) [8,18,19]. The major explanation for this discrepancy may be the difference in demographic characteristics of the populations in various studies. In this study, nearly one-half of patients were younger than 3 months, whereas previous studies have focused on patients older than 3 months. The findings in this study that a higher incidence of adverse reactions was seen in those younger than 3 months (29%) compared with those older than 3 months (19%) was particularly compatible with this explanation. Further studies involving special age groups such as premature babies, neonates, and young infants are needed to better understand the age-related safety profile of meropenem.

The high incidence of superinfection in this study (38%, 18/47) reflected the high incidence of severe underlying immunocompromised conditions (26/47). Other factors contributing to superinfection in this series were prolonged antibiotics use (31/47), the presence of central venous catheters (32/47), the presence of abdominal drainage tubes (9/47), and the placement of endotracheal tubes (31/47).

The success rate was much lower in this study than reported in other populations (81%-100% vs 72%) [7,

20]. One explanation for this discrepancy is the severity of the clinical conditions of most patients at entry of this study. Another reason is the high resistance rate and the increasing trend of resistance of bacteria to meropenem in Taiwan. About one-third of patients in this study had fatal or ultimately fatal diseases, 64% of patients were in a poor or critical condition, and 46% of patients had 2 or more sites of infection, which reflected a greater number of severe illnesses in this study compared with previous reports (64% vs 45%) [7,8]. In addition, methicillin-resistant staphylococci accounted for two-thirds of gram-positive infections in this series. It is thus not unexpected that the eradication rate of gram-positive infection was low compared with prior studies (25% vs 83%-97%) [7,8]. In contrast, the success rate of this study in treating gram-negative bacteria was also lower compared with the results reported in 1995 by Monton *et al* [7]. This finding illustrates the importance of an increased resistance rate of gram-negative bacteria to treatment success.

In summary, this study suggested that it is appropriate to use meropenem as monotherapy for serious bacterial infection in children and even in the very young population. However, the rapid increase of meropenem-resistant strains of bacteria, either gram-positive or -negative, necessitates judicious clinical use of meropenem.

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