# Efficacy and Safety of Meropenem as an Empirical Treatment for Febrile Neutropenia in Children with Cancer

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**Abstract**

Meropenem is a promising carbapenem antibiotic as an empirical monotherapy in patients with febrile neutropenia (FN). With the limited data of the therapy in pediatric patients, the authors conducted this study to evaluate the efficacy and safety of meropenem as empirical antibiotic therapy in 30 pediatric cancer patients with FN (mean age = 7.5 years), who were admitted to King Chulalongkorn Memorial Hospital from May 2000 to December 2001. Meropenem 60 mg/kg/day was given intravenously every 8 hours. The efficacy of meropenem was assessed as successful, inconclusive and failure on days 3 and 5 of the therapy and compared to that of other empirical antibiotics used from January 1997 to April 2000. The study showed that six blood culture specimens (20%) grew organisms, half of which were considered to be contaminants, and six urine culture specimens (20%) grew gram negative rod bacteria. On day 3 and 5 of the therapy, the success rate of meropenem was higher than that of comparatives (30.0% *vs* 17.6% on day 3, 50.0% *vs* 39.3% on day 5). The use of meropenem appeared safe, with minimal side effects. In conclusion, the present study showed that meropenem was safe and tolerable in children. The efficacy as an empirical monotherapy in pediatric cancer patients with FN was satisfactory, with a failure rate of 23.3 per cent on day 5 of treatment.

**Key word :** Meropenem, Febrile Neutopenia, Children

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Treatment of presumptive infections in neutropenic patients is an urgent need. Combinations of anti-pseudomonal third generation cephalosporins and aminoglycosides have been standard empirical therapy for the patients with an overall efficacy of 60-80 per cent[1]. Carbapenem antibiotics i.e. imipenem/cilastatin and meropenem, are promising candidates for an empirical monotherapy of infections in neutropenic patients because of their broad spectrum of antimicrobial activity[2-4]. There have been a few studies on the efficacy of meropenem in neutropenic children [5-10]. The objective of the trial was to evaluate the efficacy and safety of meropenem as an empirical antibiotic therapy in Thai febrile neutropenic pediatric patients.

## MATERIAL AND METHOD

Cancer pediatric patients aged 1-15 years who were treated at King Chulalongkorn Memorial Hospital between May 2000 and December 2001, and were diagnosed as febrile neutropenia (FN) were recruited into the present study. FN was defined when the body temperature (BT) was > 38.5°C for one event or > 38°C for two consecutive events within 12 hours plus the number of absolute neutrophil count (ANC) < 500 cells/mm$^3$ or < 1,000 cells/mm$^3$ and expected to decrease to 500 cells/mm$^3$ within 24 hours. Those who had received parenteral antibiotics in the previous week, were on a central indwelling catheter, had symptoms and signs of suspicion of *pneumocystis carinii* pneumonia and had a history of hypersensitivity to carbapenems were excluded. The clinical trial was approved by the Ethics Committee, Faculty of Medicine, Chulalongkorn University. After the parents or legal guardians of the subjects had signed the informed consent forms, blood for complete blood count (CBC), aspatate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), bacterial culture, urine culture and chest X-ray were performed. Meropenem at the dose of 60 mg/kg/day (not exceeding 1 g) was started intravenously every 8 hours.

Efficacy of meropenem was assessed on day 3 and day 5 of therapy. The result of therapy was classified as successful, failure and inconclusive. Successful was defined when (1) BT was < 38°C in the previous 24 hours with ANC of < 500 cells/mm$^3$ or (2) clinical improvement at the site of infection (if present). Failure was defined when (1) BT was > 39°C, (2) no clinical improvement at the site of infection (if present) or (3) if the second culture was positive. Inconclusive was defined if (1) the patient died or (2) BT < 38°C and ANC > 500 cells/mm$^3$. Success and failure rates of meropenem therapy were compared with those treated with other empirical antibiotics, reviewed from 91 episodes of FN from January 1997 to April 2000. The majority of antibiotics used in the comparative group were combinations of antibiotics with at least one 3rd generation cephalosporin (n = 51, 56.0%), one aminoglycoside (n = 36, 39.6%) or both (n = 3, 3.3%).

CBC on days 2, 3, 5 and blood culture on day 3 were performed to assess the results of the therapy. AST, ALT and LDH were performed on days 2 and 5 to assess the safety of meropenem. Side effects of meropenem and possible adverse events were recorded by physicians on days 2, 3 and 5.

## RESULTS

Enrolled into the study were thirty pediatric cancer patients with febrile neutropenia. There were 19 males and 11 females, with a mean age of 7.5 years (range 2-15 years). Types of cancers included the following: acute leukemia (24) (acute lymphoblastic leukemia, ALL = 19; acute nonlymphoblastic leukemia, ANLL = 5), lymphoma (3) (Hodgkin lymphoma = 1, Non-Hodgkin lymphoma = 2), yolk sac tumor (1), retinoblastoma (1) and histiocytosis (1).

Possible sites of infection included the respiratory tract (5) (bronchitis = 4, upper respiratory tract = 1), oral cavity (5) (mucositis = 3, dental caries = 1, root abscess = 1), myositis (1) and gastrointestinal tract (diarrhea = 1). Eighteen cases had no evidence of infection sites.

On day 3 of meropenem therapy, the results were classified as successful (n = 9, 30.0%), inconclusive (n = 6, 20.0%) and failure (n = 15, 50.0%). On day 5 of therapy after excluding 6 inconclusive cases on day 3 of therapy, the results were classified as successful (n = 12, 50.0%), inconclusive (n = 5, 20.8%) and failure (n = 7, 29.2%) (Fig. 1). The success rates on days 3 and 5 of meropenem were higher than those of other antibiotic therapies (30.0% *vs* 17.6% on day 3 and 50.0% *vs* 39.3% on day 5). The successful, inconclusive and failure rates of meropenem and other antibiotic therapies are summarized in Table 1. Seven cases failed to respond to meropenem on day 5.

Blood culture was positive in 6 patients (20%) i.e. streptococcus group G (1), *Staphylococcus aureus* (1), coagulase negative staphylococcus (1), micrococcus (1), bacillus (1) and *Escherichia coli* (*E. coli*) (1). Urine culture was positive in 6 patients (20%) i.e.

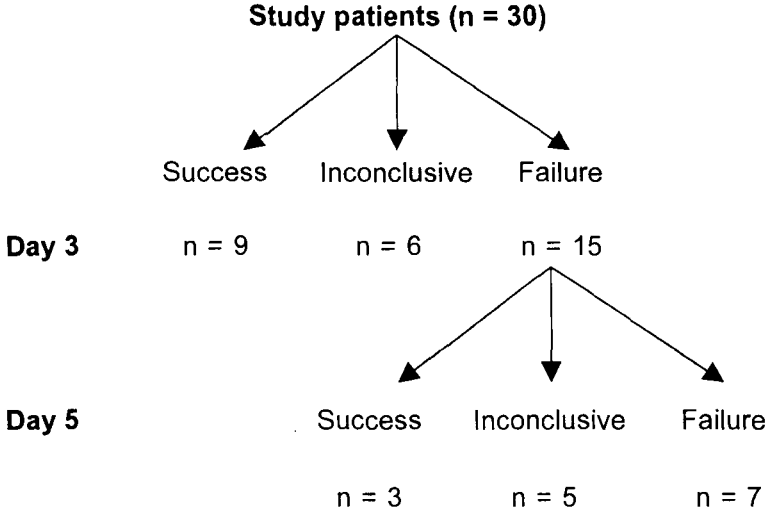


**Fig. 1. Results of meropenem in pediatric cancer patients with febrile neutropenia on days 3 and 5 of therapy.**

**Table 1. Results of meropenem and other antibiotic therapy in pediatric cancer patients with febrile neutropenia on days 3 and 5 of therapy.**

| Day of therapy | Success | | | | Inconclusive | | | | Failure | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Meropenem | | Others | | Meropenem | | Others | | Meropenem | | Others | |
| | No | % | No | % | No | % | No | % | No | % | No | % |
| Day 3 | 9 | 30.0 | 16 | 17.6 | 6* | 20.0 | 2* | 2.2 | 15** | 50.0 | 73*** | 80.2 |
| Day 5 | 12 | 50.0 | 35 | 39.3 | 5 | 20.8 | 15 | 16.9 | 7 | 29.2 | 39 | 43.8 |

Note : * This number of patients were not included in denominators on day 5 of the therapy.
** 5 patients were changed to inconclusive group and 3 patients were changed to success group on day 5 of meropenem therapy.
*** 39 patients were changed to inconclusive group and 19 patients were changed to success group on day 5 of other antibiotic therapy.

*Acinetobacter* spp (1), *Klebsiella* spp (1), *Morganella morganii* (1), *E. coli* (1), *Pseudomonas aeruginosa* (*P. aeruginosa*) (1) and *Enterobacter* spp (1).

Possible side effects of meropenem included diarrhea (1) and rash (1), which were mild, transient and self-limited. There was no significant change of the levels of AST, ALT and LDH.

## DISCUSSION

The present study showed that meropenem as an empirical monotherapy in pediatric cancer patients with FN confirmed the previous studies as having a satisfactory rate of success[9,10]. Meropenem used in these studies had a slightly higher success rate compared to the use of other antibiotics in the present study and previous studies[7,9,10]. The assessment of the response to antimicrobial treatment was complicated by several factors. Therefore, the rates of success varied among the studies and were difficult to compare. Even though the meropenem therapy yielded a low success rate on day 3 of the therapy (30.0%), after continuing the same treatment, 5 out of 15 patients (33.3%) in the failure group responded to the treatment on day 5. Therefore, the authors recommend no change of the antibiotic treatment until day 5 of the therapy unless the condition of the patient worsens.

Moreover, 6 inconclusive cases on day 3 and 5 inconclusive cases on day 5 of the therapy also became afebrile with ANC > 500 cells/mm$^3$, adding 11 more cases with a favorable outcome.

In the present study, the authors monitored biochemical profiles (AST, ALT, LDH) and adverse events within a few days of therapy. As reported in previous reports[5,6,9,10], it was found that meropenem was well tolerated and there was no significant change of the profiles. Minimal side effects were found and none of them were serious or had clinical importance.

The initial therapy to treat presumptive infections in neutropenic patients is empirical based on pathogens that are most likely responsible for the patient's rise in temperature or other symptoms of infection. In most developing countries, the upsurge of infections in the 1970s and 1980s caused by gram-negative organisms, particularly *P. aeruginosa*, *E. coli* and *Klebsiella* spp, was supplanted by a new wave of infections caused by gram-positive organisms[1,7]. In Thailand, however, recent studies showed that gram-negative bacteria including *Salmonella* spp. were predominant in positive blood cultures among neutropenic patients[11-13], probably because of the limitation of the use of central indwelling catheters.

The potential advantage of meropenem over the available parenteral cephalosporins is its exceptionally broad spectrum of antimicrobial activity. This permits a single agent of empirical therapy in the treatment of a wide range of pediatric infections, particularly those in whom a polymicrobial etiology is suspected. At present, the authors do not recommend the use of meropenem as an alternative drug in neutropenic patients in Thailand. The combination of antibiotics such as anti-pseudomonal cephalosporins plus aminoglycosides would be appropriate in covering the majority of bacteria in patients. Meropenem should be preserved for those who have a high suspicion of gram-positive infection or those who do not respond to the first-line drugs.

In summary, the present study showed that the efficacy of meropenem as empirical monotherapy in pediatric cancer patients with FN was satisfactory, with failure rates of 50.0 per cent on day 3 of treatment and 29.2 per cent on day 5 of treatment. The drug is tolerable and safe in children, with minimal and non-serious side effects.

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# การศึกษาประสิทธิภาพและความปลอดภัยของการใช้ยาต้านจุลชีพเมโรพีเน็มเป็นยาเบื้องต้นในการรักษาเด็กที่ป่วยเป็นมะเร็งและมีไข้ร่วมกับภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำ

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เมโรพีเน็มเป็นยาต้านจุลชีพกลุ่ม carbapenem ซึ่งเป็นที่ยอมรับให้ใช้เป็นยาเบื้องต้นในการรักษาไข้ร่วมกับภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำ เนื่องจากความจำกัดของข้อมูลในการรักษาผู้ป่วยเด็ก ผู้วิจัยจึงทำการศึกษาเพื่อประเมินประสิทธิภาพและความปลอดภัยของยาเมโรพีเน็ม ในการรักษาเด็กที่ป่วยเป็นโรคมะเร็ง มีไข้ร่วมกับภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำและรับการรักษาที่โรงพยาบาลจุฬาลงกรณ์ ระหว่างเดือนพฤษภาคม 2543 ถึงเดือนธันวาคม 2544 จำนวน 30 คน (อายุเฉลี่ย 7.5 ปี) ขนาดของยาเมโรพีเน็มที่ให้คือ 60 มก/กก/วัน แบ่งให้ทางเส้นเลือดทุก 8 ชม ทำการประเมินประสิทธิภาพของยาในวันที่ 3 และ 5 ของการรักษาโดยจำแนกผลการรักษาเป็น 3 กลุ่มคือ ประสบความสำเร็จ ไม่สามารถสรุปได้ และประสบความล้มเหลว และทำการเปรียบเทียบกับการรักษาด้วยยาต้านจุลชีพอื่น ระหว่างเดือนมกราคม 2540 ถึงเดือนเมษายน 2543 พบว่า เพาะเชื้อขึ้นในตัวอย่างเลือด 6 ตัวอย่าง (ร้อยละ 20) โดย 3 ตัวอย่างอาจเป็นเชื้อที่ปนเปื้อน และเพาะเชื้อในปัสสาวะขึ้นเชื้อแบคทีเรียกรัมลบทรงแท่ง 6 ตัวอย่าง (ร้อยละ 20) ในวันที่ 3 และ 5 ของการรักษา อัตราความสำเร็จของยาเมโรพีเน็มสูงกว่ากลุ่มเปรียบเทียบ (ร้อยละ 30 *vs* 17.6 ในวันที่ 3 และร้อยละ 50 *vs* 39.3 ในวันที่ 5 ของการรักษา) ยามีความปลอดภัยสูงและมีผลข้างเคียงเล็กน้อย สรุปได้ว่า ยาเมโรพีเน็มเป็นยาต้านจุลชีพที่มีความปลอดภัยและใช้ได้ในผู้ป่วยเด็ก ประสิทธิภาพของยาในการใช้เป็นยาเบื้องต้นในการรักษาผู้ป่วยเด็กมะเร็งที่มีไข้ร่วมกับภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำเป็นที่น่าพอใจ โดยพบอัตราล้มเหลวคิดเป็นร้อยละ 23.3 ในวันที่ 5 ของการรักษา

**คำสำคัญ** : เมโรพีเน็ม, ภาวะไข้และเม็ดเลือดขาวนิวโตรฟิลต่ำ, เด็ก

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