Original Articles/นิพนธ์ต้นฉบับ

Study on the Anti-Infectious Efficacy of the Generic Drug Meropenem (Enem®) in Treating Patients with Serious Infections.

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Abstract

Introduction: Meropenem, a carbapenem antibiotic, displays a broad spectrum of antibacterial activity against gram positive, gram negative and anaerobe bacteria. It plays an important role in a treatment of multidrug resistant nosocomial infections. However, patients with such indication still have low accessibility to meropenem due to the high cost of the meropenem original drug. Therefore, generic meropenem, such as ENEM®, was developed in order to reduce therapeutic cost.

Objective: The purpose of this study was to evaluate antibacterial efficacy of meropenem in a treatment of severe bacterial infections.

Method: An open-labeled non-randomized matched case-control trial was performed at Somdejprapinklao Hospital. Thirty seven patients diagnosed with severe bacterial infection or high risks in nosocomial infections caused by bacteria sensitive to meropenem volunteered in this study. The clinical and micro-biological responses of the treatment group were matched with those of control group with similar clinical manifestations treated by meropenem and other regimens.

Results: Results showed that 15 patients (51.4%) who were treated with ENEM® were not found microorganism at the infected sites. And 21 patients (56.8%) who were treated with ENEM® were cured based on clinical evaluation. In addition, serum albumin and serum globulin of patients in the treatment group were significantly higher than those of patients in the control group (p=0.033 and 0.043, respectively). No difference in blood levels of blood urea nitrogen (BUN), creatinine, hepatic enzymes, and electrolytes among patients in the treatment and control groups implied that ENEM® caused no serious adverse effects.

Conclusion: This study confirmed antibacterial efficacy and safety of ENEM® in a treatment of severe bacterial infections in hospitals.

Keywords: Meropenem, ENEM®, efficacy

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Introduction

Meropenem, which is one of the antibiotics in carbapenem group, has a broad spectrum of anti-bacterial activity against a wide range of gram positive, gram negative and anaerobe bacteria including Enterobacteriaceae producing extended-spectrum-lactamase (ESBL) and AmpC which are courses of multidrug resistant nosocomial infections[1]. Meropenem is approved for treatments of complicated intra-abdominal infection (cIAI), complicated skin and skin structure infection (cSSSI) and bacterial meningitis (in children above the age of 3). Additional indications of meropenem are hospital-acquired pneumonia, sepsis, febrile neutropenia, urinary tract infections, obstetric infections, cystic fibrosis and severe community-acquired pneumonia (CAP)[2-4]. Meropenem exhibits bactericidal activity by binding to penicillin binding protein (PBPs) leading to inhibition of peptidoglycan transpeptidation and resulting in interruption of intact bacterial cell-wall synthesis. Thus, meropenem stops bacterial growth and causes cell death.[3] Meropenem shows low plasma protein binding (~2%). It well penetrates throughout body tissues such as lung, interstitial fluid, peritoneal and spinal fluid. Meropenem is eliminated through renal excretion without future transformation; therefore, dose adjustment in renal failure patients is not necessary. In patients with normal renal functions, meropenem possesses a short half life of about 1 hour. A 3-times-daily dosing regimen is recommended in order to maintain drug plasma concentration at an appropriate level. Meropenem antibacterial activities are time-dependent. Drug concentration at the infected sites must higher than the minimum inhibitory concentration (MIC) in order to terminate bacterial growth, %T>MIC[3,4]. Meropenem is well tolerated by patients. Adverse drug reactions include nausea and vomiting with low incidence of nervous system side effects comparing with other carbapenems.

Antibiotics with high efficacy and low side effects are necessary in a treatment of severe bacterial infections in order to increase patient survival rate and decrease incident of recurrent bacterial infections[7]. The use of inappropriate antibiotics results in microbial resistance and treatment failures. Antibiotics in a treatment of nosocomial infections are carbapenems, aminoglycosides, quinolones and cepholosporins. Properties of each antibiotic group differ from others in terms of antibacterial spectrum, dose and dosing frequency. Meropenem is a broad spectrum carbapenem which is resistant to dehydro-peptidaseand β-lactamases particularly penicillinases andcephalosporinases. It is well distributed throughout the body; therefore, it is an appropriate drug of choice in both an empirical and a definite treatment of nosocomial infections[4]. Patients with indications have limited access to meropenem original drug due to its high cost; therefore, bioequivalent generic meropenem with affordable price such as ENEM® is developed and formulated to reduce treatment cost and increase drug accessibility to patient[9]. The objectives of this study are to determine therapeutic efficacy and adverse side effects of ENEM® in a treatment of severe nosocomial infections.The therapeutic efficacy of ENEM® was supported by microbiological and clinical response data of ENEM® with no observed-severe side effects. Finally, ENEM® will be confidently prescribed in a treatment of severe nosocomial infection by health care providers.

Methods

Drug efficacy study

In this study, antibacterial efficacy of ENEM® in a treatment of severe bacterial infected patients, at Somdejprapinklao Hospital during November 1, 2007 to April 30, 2008, was performed according to an open-labeled non-randomized matched case-control trial and evaluated from microbiological and clinical

responses. The clinical trial protocol was approved by The Sciences and Ethical Review Committee for Research in Human Subjects (SiEC protocol number 403/2549) and conducted according to its guidelines. Volunteers in this study were patients with severe bacterial infections or patients with risks in multidrug resistant nosocomial infections who were prescribed meropenem treatment.

In this study, volunteers were divided into 2 groups, control and study groups. The control group was divided into 2 subgroups definitive and empirical treatment groups. Volunteers in the definitive treatment group were patients diagnosed with pneumonia or urinary tract infection (UTI) caused by bacteria sensitive to meropenem. Volunteers in the empirical treatment group were patients diagnosed with pneumonia UTI or sepsis to severe sepsis before the real cause of infection was confirmed. Risk assessment of infections due to multidrug resistant strains was performed based on the following conditions; patients who were admitted in the hospital for more than 5 days; patients with a history of broad spectrum antibiotics administration especially 3rd generation cepharosporins or fluocinolones in the last 3 months; patients who stay in a nursing home; dialysis patients; patients with low immune status or on immunosuppressive drugs; patients on respirator for more than 72 hours; patients with catheter-related infections, i.e catheter-related UTI, catheter associated sepsis or patients with feeding tube for more than 72 hours and/or patients with one of the following risk factors, i.e. patients with a record of ESBL-producing *E. coli* infection in the last 12 months, diabetic patients, patients with cerebral paralysis and a record of infection in the last 12 months. Exclusion criteria were penicillins- or cephalosporins-allergic patients, patients with liver disease, patients with end-state kidney disease or patients in shock. Volunteers in the control group were patients with medical records of severe infections whose ages were within plus or minus 5 years to that of patients in the study group. In addition, the matching was done so that volunteers in both groups had the same gender and similar clinical manifestations. The prescribed antibiotics regimens and therapeutic outcomes, such as duration of fever after taking antibiotics to be subside, clinical responses (cure or death), duration of hospitalization, resistance of the isolated-pathogens, and responses of the pathogens to the prescribed antibiotics, were recorded.

In this study, the volunteers in the study group were intravenously infused ENEM® over 30 minutes. ENEM® dosing regimens were depended up on the following indications. Half gram of ENEM® was given every 8 hours for hospital-acquired pneumonia. One gram of ENEM® was given every 8 hours for septicemiaorfebrile neutropenia due to infections. And 2 grams of ENEM® were given every 8 hours for meningitis. Physical examination and vital signs were examined by physicians. On day 0, 3, 7, 10 and 14 blood samples were collected in order to evaluate clinical responses and adverse side effects from CBC, blood urea nitrogen (BUN), creatinine, SGOT, SGPT and blood electrolytes levels. If the therapeutic outcomes on day 14 were not improved, blood samples would be further collected and evaluated on day 28.

Clinical response evaluations

Improvement of clinical responses at the infection sites was evaluated on day 3, 7, 14 and 28 by evaluation of body temperature or some specific clinical symptoms such as absence of abscess, urine clarity, or no sign of infection in radiograph. Evaluation criteria were as follows; cure, improvement, deterioration, or death from infections or other specified causes.

Microbiological response evaluations

Swabs at the infection sites were re-cultured on day 7 and 14. If bacterial culture was positive on day 14, the infection sites were re-swabbed on day

28. Evaluation criteria were as follows; cure (negative bacterial culture), improvement (less bacterial colony on the culture) and deterioration (positive bacterial culture).

Statistical analysis

Student t test and chi-square ($\chi 2$) test (α = 0.05) were employed in descriptive analysis of therapeutic outcomes using SPSS software version 10.0.

Results

Drug efficacy study

Seventy five patients with severe nosocomial infections were included in the study (Table 1). Number of volunteers in the study and the control groups were 37 and 38, respectively, with age range of 54-90 years old. Majority of the patients in both groups were diagnosed with pneumonia and UTI.

Physicians prescribed empirical antibiotic treatment on 22 (59.5%) and 27 (71.0%) patients in the study and control groups, respectively. During the study, 32 out of 75 patients or 42.67% of patients passed away. In details, 15 out of 37 patients (40.54%) in the study group and 17 out of 38 patients (44.74%) in the control groups died. Causes of death were bacterial infections (n=29) and other causes such as upper gastrointestinal hemorrhage (UGIH, n=1), pulmonary embolism (PE, n=1) and heart failure (n=1).

Clinical response evaluations

Clinical responses (based on body temperature or some specific clinical symptoms such as absence of abscess, urine clarity, or no sign of infection in radiograph) showed that, on day 3, one patient in the control group was curewhile none in the study group was cure. The observed healing on day 3 was insignificant difference between the 2 groups although patients in the study groups seemed to show better responses to the treatment than patients in the control group (Table 2, Figure 1). At day 7, more patients in the study groups showed worse clinical responses than day 3. However, after clinical response evaluation

Table 1 Demographic and clinical data of volunteers.

	ENEM® (n=37)	Control group (n=38)	p-value
Gender, male/female	12/25	23/15	0.015
Age (years)	72.8±12.7	70.1±16.1	0.426
Clinical diagnosis			0.719
pneumonia	21	24	
UTI	11	6	
sepsis	4	4	
bacterial infections of reproductive system	1	2	
skin infection	0	1	
peritoneal infection	0	1	
Patients withSIRS*	33	35	0.664
Number of ICU patients	3	16	0.001
Number of kidney failure patients	13	12	0.744

*Patients were diagnosed with SIRS when patients showed more than 2 signs of the following symptoms, i.e. body temperature >38 or <36°C, heart rate >90 bpm, respiratory rate >20 times/min or PaCO2 <32 mmHg, WBC >12,000 or <4,000 /mm^3 or >10% band forms.[10,11]

Table 2 Clinical responses of patients

Clinical responses	Number of patientsin each groups							
	Day 3		Day 7		Day 14		Day 28	
	ENEM®	Control	ENEM®	Control	ENEM®	Control	ENEM®	Control
cure	0	1	13	13	20	14	21	17
improve	20	24	8	8	-	-	-	-
stable	13	0	4	0	2	5	0	1
worse	4	9	9	9	6	5	1	3
death from infection	0	4	0	1	9	12	14	15
Death from other causes	-	-	-	-	0	2	1	2
Total	37	38	37	38	37	38	37	38

on day 14 and 28, the results suggested that number of cure patients in the study group, which administered ENEM®, were higher than that of in the control group.

Microbiological response evaluations

Table 3 shows pathogens at the swab sites including blood, mucus, urine and tissues at the infected sites at the beginning of the study. Re-cultured results from day 7 showed that the empirical antibiotic treatment for 4 and 3 patients in the study and control groups, respectively, was not in accordance with their microbial susceptibility. In the study group, there were 19 and 3 patients who were cure (negative bacterial culture) and showed improvement (less bacterial colony on the culture), respectively.While, 8 and 4 patients in the control group were cure and showed improvement, respectively.

The re-cultured results from day 14 indicated that 13 patients infected with the secondary pathogens, i.e. K. pneumoniae (n=2 or 5.4%) and A. baumannii (n=11 or 29.7%). After diagnosis with the secondary infections, the patients were treated with

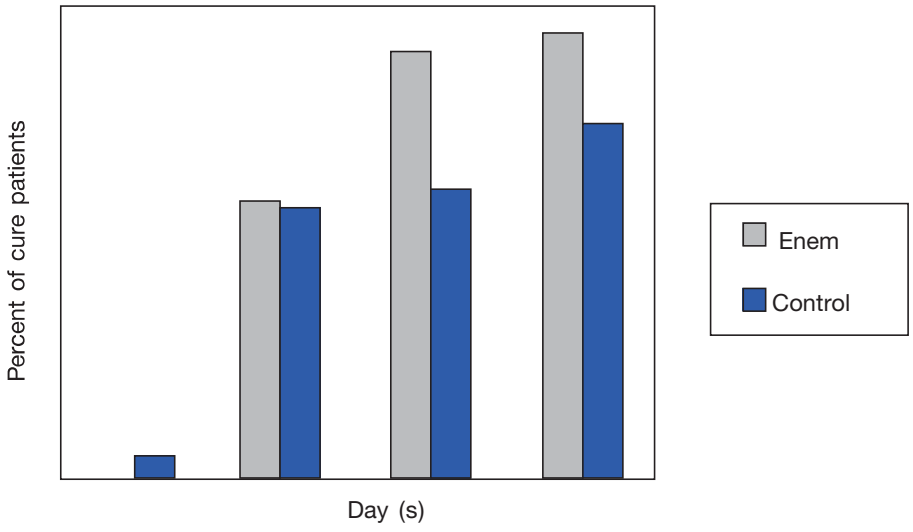

Figure 1 *percent of cure patients based on clinical responses at the infected sites.*

Table 3 Pathogens and number of patients infected by the pathogens at the beginning of the study.

Pathogens	Number of patients in each groups	
	ENEM®	control
E. coli	1	1
E. coli ESBL+*	13	5
K. pneumoniae	1	4
K. pneumoniae ESBL+*	1	1
P. aeruginosa	5	10
A. baumannii	9	4
Group D streptococci	1	0
MRSA**	0	1
MR-CoNS***	0	1
P. vulgaris	0	1
No infection	6	6
No data	0	4

* ESBL+: bacteria that the producedextended-spectrum β-lactamase enzyme

** MRSA: methicillin-resistant Staphylococcus aureus

*** methicillin resistant coagulase negative Staphylococcus

an antibiotic or a combination of antibiotics susceptible to those microorganisms. However, there was no report on secondary infection in the control group.

Discussions

Drug efficacy study

Based on the demographic and clinical data, both groups were insignificantly difference in age, causes of infections, number of patients with systemic inflammatory response syndrome (SIRS), and number of patients with kidney failure. Blood urea nitrogen (BUN), creatinine, SGOT, SGPT, and blood electrolyte levels of patients in both groups were insignificantly different from each other throughout the study. However, gender and severity of patient's conditions between the two groups were differences. Number of male patients in the study group was significantly higher than that of in the control group with p=0.015. Number of ICU patients in the study group was significantly lower than that of in the control group with p=0.001. CBC values on day 1 showed that white blood cells of patients in the study group were significantly lower than that of in the control group (12,862±5,319 and 18,028±10,847 cell/mm^3, respectively; p=0.014). However, by the end of the study, levels of white blood cells in both groups were insignificantly different from each other (13,762±3975 and 12,220±2872 cell/mm^3, respectively; p=0.353). Moreover, patients in the study group showed significant increase in levels of serum albumin and serum globulin with p=0.033 and 0.043, respectively. All 29 patients who died from bacterial infections (14 and 15 patients in the study and control groups, respectively) were diagnosed with severe infections or infections from multidrug resistant bacteria. Thus, it was highly likely that these patients could not be easily cured with other antibiotics treatments including meropenem.Therefore, ENEM® treatment gave not only satisfied clinical responses for patients with bacterial infections when compared with treatments in the

control groups but also resulted in an increase of plasma proteins.

Conclusions

Treatment of severe bacterial infections or multidrug resistant nosocomial infections needs to use antibiotics which possessed high efficacy and low side effects. This study illustrates that ENEM®, a generic meropenem, tends to show better efficacy in the treatment of bacterial infections than treatments in the control group based on clinical and microbiological responses. ENEM® treatment results in an increase of serum albumin and serum globulinwithout severe side effects based on normal blood levels of blood urea nitrogen, creatinine, SGOT, SGPT, and blood electrolytes throughout the study. Although number of volunteers in this study was limited and the study design was not a randomized controlled clinical trial, the results obtained from this study confirmed efficacy and safety of ENEM® in a treatment of severe nosocomial infections. Thus, physicians can prescribe ENEM® with confidence and hopefully increase patient accessibility to this drug.

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