J Infect Chemother xxx (2014) 1–6

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original article

Open-label study to evaluate the pharmacodynamics, clinical efficacy, and safety of meropenem for adult bacterial meningitis in Japan

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ARTICLE INFO

Article history:
Received 28 December 2013
Received in revised form
6 March 2014
Accepted 28 April 2014

Keywords:
Meropenem
Bacterial meningitis
Efficacy
Safety
Japanese
Adult

ABSTRACT

The aim of this study was to assess the efficacy, safety, and concentration of meropenem in cerebrospinal fluid when meropenem (2 g every 8 h) was administered to Japanese adult patients with bacterial meningitis. Five Japanese patients (mean age 60.6 years [range 35–71]) were enrolled. Infection with *Streptococcus pneumoniae* (three patients), *Streptococcus salivarius* (one patient), and *Staphylococcus aureus* (one patient) was confirmed by cerebrospinal fluid culture. Meropenem (2 g every 8 h) was administered to all five patients. Treatment duration ranged from 14 to 28 days (mean 22.6 days). All the patients were successfully treated. The concentration of meropenem in cerebrospinal fluid ranged from 0.27 to 6.40 μg/ml up to 8.47 h and was over 1 μg/ml 3 h after starting meropenem infusion. In each patient, the present study confirmed for the first time that the concentration of meropenem in cerebrospinal fluid exceeded the minimal inhibitory concentration for these pathogens. Eleven clinical and laboratory adverse events considered to be related to meropenem were observed in all patients, but no serious adverse event and no discontinuance of treatment due to adverse events occurred. Thus meropenem appeared to be a well-tolerated and effective agent for Japanese adult patients with bacterial meningitis. 2 g every 8 h of meropenem was delivered to CSF and its concentration was exceed in MICs for the detected pathogens.

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http://dx.doi.org/10.1016/j.jiac.2014.04.013
1341-321X/

1. Introduction

Meropenem (MEPM) is a parenteral carbapenem antibiotic which has highly potent bactericidal activity *in vitro* against almost all clinically significant aerobes and anaerobes. Its high activity is explained by ease of entry into bacteria combined with good affinity for essential penicillin binding proteins, including those associated with cell lysis.

Bacterial meningitis is associated with high rates of morbidity and mortality. Bacterial meningitis has an annual incidence of 1.38–2.6 cases per 100,000 patients, and *Streptococcus pneumoniae* and *Neisseria meningitidis* are responsible for 80 percent of all cases [1,2]. Early diagnosis and treatment are essential because delay in the initiation of antimicrobial therapy leads to poor outcome in this disease. The rate of pneumococcal meningitis due to penicillin-resistant *S. pneumoniae* is more frequent in Japan than in the United States where antibiotic-resistant *S. pneumoniae* strains are highly prevalent, and pneumococcal meningitis due to penicillin-resistant *S. pneumoniae* has emerged as a major problem in the treatment of patients with bacterial meningitis [2–4]. Third-generation cephalosporins are the established empiric agents of choice in Europe for pneumococcal meningitis. When penicillin or cephalosporin resistance is possible then vancomycin (VCM) should be combined with a third-generation cephalosporin [5,6]. On the other hand, in the United States, administration of VCM plus a third-generation cephalosporin is recommended because penicillin-resistant pneumococcal meningitis is highly prevalent [7]. The Infectious Disease Society of America (IDSA) guidelines (2004) and European Federation of Neurological Sciences (EFNS) guidelines (2008) describe MEPM as the alternative empirical antibiotic therapy for suspected acute bacterial meningitis [6,7]. However, no report has assessed the concentration of MEPM in cerebrospinal fluid (CSF) when 2 g every 8 h of MEPM is administered in adult patients with bacterial meningitis. The aim of this study was to measure the concentration of MEPM in CSF and to confirm the safety and efficacy of MEPM in the therapy of bacterial meningitis in Japanese adult patients.

2. Patients and methods

2.1. Study design

This study was a multicenter, non-comparative and non-blinded clinical trial evaluating the pharmacodynamics, clinical safety, and efficacy of MEPM in Japanese adults with bacterial meningitis. It included 12 medical institutions in Japan and was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines in Japan; the study protocol was approved by the institutional review boards (IRBs) of all 12 medical institutions. IRB-approved informed consents were received from all subjects or their legal representatives before the initiation of the study.

2.2. Patients

Japanese adult patients with strongly suspected or documented bacterial meningitis were enrolled prospectively. The study included patients 1) who were admitted with symptoms or evidence of bacterial meningitis such as fever, nuchal rigidity, impaired consciousness, etc., and confirmed to be infected with the bacterium by CSF culture, CSF Gram stain, bacterial antigen test, or positive CFS test results for bacterial meningitis; 2) who were 16 years old or more when their informed consent was obtained; 3) who were hospitalized; 4) from whom the written informed consent was obtained in accordance with the IRB-

Table 1
Patient characteristics.

	Age (years old)	Sex	Body temperature (°C)	Neck stiffness	GCS	CSF					WBC (/μl)	CRP (μg/100 ml)	Pathogen	MIC to MEPM (μg/ml)	Duration of treatment (days)	Bacteriological response	Outcome at EOT
						Cell count (/μl)	Polymorphonuclear cells (%)	Glucose (mg/100 ml)	CSF/plasma glucose	Protein (mg/100 ml)							
Patient 1	79	F	39.5	Yes	7	2300	76.8	4	0.03	462.8	18,420	0.648	*S. salivarius* (CSF)	≤0.06	28	Eradicated	Effective
Patient 2	61	F	36.3	Yes	11	248	[a]	0	0.00	439	6600	17.01	*S. pneumoniae* (Blood)	≤0.06	28	Eradicated	Effective
													S. pneumoniae (CSF)	≤0.06			
Patient 3	64	F	36.3	Yes	15	472	90	2	0.01	436	16,000	22.95	*S. pneumoniae* (CSF)	≤0.06	14	Eradicated	Effective
Patient 4	35	M	38.2	Yes	9	720	90	77	0.51	122	63,200	18.27	*S. aureus* (Blood)	≤0.06	21	Eradicated	Effective
													S. aureus (CSF)	0.12			
Patient 5	64	M	38.9	Yes	6	1965	98.4	0	0.00	556	33,400	20.36	*S. pneumoniae* (CSF)[b]	≤0.06	22	Eradicated	Effective

CRP, C-reactive protein; CSF, cerebrospinal fluid; GCS, Glasgow coma scale; MEPM, meropenem; MIC, minimal inhibitory concentration; EOT, end of treatment; WBC, white blood cell.
[a] Mostly polymorphonuclear cells.
[b] CSF Gram stain revealed Gram-positive bacteria.

Please cite this article in press as: Morita A, et al., Open-label study to evaluate the pharmacodynamics, clinical efficacy, and safety of meropenem for adult bacterial meningitis in Japan, J Infect Chemother (2014), http://dx.doi.org/10.1016/j.jiac.2014.04.013