Drug Substance	Meropenem	**SYNOPSIS**	(For national authority use only)
Study Code	3591US/0031		
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A Study to Assess the Concentration of Meropenem in Epithelial Lining Fluid, Pulmonary Alveolar Cells, and Plasma Following the Intravenous Administration of Multidoses to Healthy Subjects

Investigator

Study center

This study was conducted at 1 center.

Study dates		**Phase of development**
First subject enrolled	8 June 2001	Clinical pharmacology (I)
Last subject completed	4 August 2003	

Objectives

The primary objective of this study was to measure and compare the concentration of meropenem in (intrapulmonary) epithelial lining fluid (ELF), pulmonary alveolar cells (ACs), and plasma following multiple dose regimens of meropenem: 500, 1000, or 2000 mg intravenously (iv) every 8 hours (x 4 doses). The secondary objective was to assess safety, measured in terms of spontaneous adverse events (AEs), subjective symptoms, clinical laboratory measurements, vital signs, and fingertip oximetry.

Study design

This was a single-center, multiple-dose, open-label study involving 3 dosages of meropenem (described in the objectives paragraph). Subjects assigned to treatment with 500 or 1000 mg were subdivided into 5 groups of 4 subjects each, and subjects assigned to treatment with 2000 mg were subdivided into 2 groups of 4 subjects each. Within a dose group, subgroups were distinguished from each other by the time at which subjects were scheduled to undergo bronchoalveolar lavage (BAL).

Each of 4 planned doses of meropenem was administered by iv infusion over 30 minutes. After the 4th infusion was completed, subjects underwent BAL at 1, 2, 3, 5, or 8 hours after the start of that infusion depending on the subgroup to which they were assigned. Blood

samples were obtained immediately after the last meropenem infusion and immediately after the BAL procedure for determination of meropenem concentration.

Target subject population and sample size

Healthy men and women aged 18 to 45 years with a body mass index (BMI) between 18 and 29 and no contraindications relative to medical and drug history, physical examination results, vital signs measurements, or clinical laboratory test results were eligible for enrollment. Women could not be pregnant and had to abstain from sexual intercourse during the study or alternately use a barrier method or oral contraceptives during and for 1 month after the study. Approximately 50 subjects were sought for study enrollment. The target sample size was not based on power calculations. Instead, it was a practical determination that included estimates of pharmacokinetic variability and attempts to reduce the number of bronchoscopy procedures.

Investigational product: dosage, mode of administration, and batch numbers

Meropenem was supplied as a dry powder for reconstitution in 500 mg/20-mL injection vials (Formulation number F7145).[1] After reconstitution, prescribed doses were diluted to a final volume of 250 mL and infused over 30 minutes.

Duration of treatment

Given the treatment regimen used (1 dose every 8 hours for 4 doses), the duration of treatment was slightly greater than 1 day.

Variables

- **Pharmacokinetics**

  Primary variables: meropenem concentrations in ELF, ACs, and plasma.

- **Safety**

  Secondary variables: spontaneously reported AEs, subjective symptoms, clinical laboratory measurements, vital signs, and fingertip oximetric measurements.

Statistical methods

Following the determination of meropenem concentration in ELF, ACs, and plasma, ratios of meropenem concentrations were determined for ELF/plasma and AC/plasma. Concentration data and their ratios were summarized by appropriate descriptive statistics. Adverse events were summarized by body system and preferred term (Medical Dictionary for Regulatory Activities [MedDRA] terminology). Other safety assessments were summarized descriptively.

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[1]The protocol provided for the potential to prepare assigned doses using 500 mg/100-mL iv infusion vials (Formulation number F12260), but none were requested or supplied.

Subject population

A total of 42 subjects were treated with meropenem at either the 500-mg dose (n=21) or the 1000-mg dose (n=21); 8 of those subjects were also treated at the 2000-mg dose for a total of 50 subjects treated. All but 1 subject completed treatment as planned. One subject had pruritus after her first 500-mg dose and was subsequently withdrawn. A summary of subject demographic characteristics is provided in Table S1.

Table S1 Subject population

Characteristics		Meropenem treatment group					
		500 mg (n=21)		1000 mg (n=21)		2000 mg (n=8)	
Demographic characteristics							
Sex, No. (%)	Male	10	(48)	12	(57)	5	(63)
	Female	11	(52)	9	(43)	3	(38)
Age (years)	Mean (SD)	32.5	(7.0)	29.0	(5.5)	32.4	(7.2)
	Range	23 to 44		18 to 42		25 to 45	
Race, No. (%)	White	12/10[a]	(57)/(48)	16	(76)	4	(50)
	Black	2	(10)	1	(5)	1	(13)
	Asian	5	(24)	2	(10)	1	(13)
	Hispanic	1	(5)	0		0	
	Other[b]	1/3[a]	(5)/(14)	2	(10)	2	(25)
Height (cm)	Mean (SD)	171	(9)	173	(10)	175	(10)
Weight (kg)	Mean (SD)	68	(10)	72	(13)	74	(13)

[a] Two subjects classified as *white* when enrolled for treatment at the 500-mg dose were later classified as *other* when re-enrolled at the 2000-mg dose. Data queries confirmed that o*ther* was correct, which changes the number of white subjects to 10 and the number of o*ther race* subjects to 3 at the 500-mg dose. This change is not reflected in the source table (Table T2.1) for reasons related to the decommissioning of the original database.

[b] Includes subjects of mixed race and other nonspecified races.

Summary of pharmacokinetic results

Pharmacokinetics data are provided in Appendix 12.1.13.

Summary of safety results

All subjects in each meropenem treatment group reported at least 1 AE. AEs most commonly fell within the MedDRA SOC categories of respiratory disorders and general disorders (Table S2). Rales, the AE most frequently reported after each treatment, occurred in 17 (81%), 10 (48%), and 4 (50%) subjects treated at the 500-, 1000-, and 2000-mg doses, respectively. Most AEs were characterized as mild. The exceptions—pyrexia (at 500 mg), cough (at 1000 mg), and fatigue (at 2000 mg)—were each characterized as moderately intense. As assessed by the investigator, AEs were predominantly related to BAL procedures and not

exposure to meropenem. Only 7 AEs were considered drug-related by the investigator: pruritus (subject withdrawn) at the 500-mg dose; nausea, flatulence, moderate pyrexia, and headache at the 1000-mg dose (in 1 subject each); and epistaxis and nausea at the 2000-mg dose (in 1 subject each).

Table S2 Adverse events by treatment group

MedDRA system-organ class and preferred term		Treatment					
		Meropenem 500 mg (n=21)		Meropenem 1000 mg (n=21)		Meropenem 2000 mg (n=8)[a]	
Ear and labyrinth disorders	Tinnitus	1	(5)	0		0	
Gastrointestinal disorders	Diarrhea, NOS	2	(10)	0		0	
	Flatulence	0		1	(5)	0	
	Nausea	0		3	(14)	1	(13)
General disorders	Chest pain	0		3	(14)	0	
	Fatigue	0		2	(10)	1	(13)
	Pain/pain, NOS	0		2	(10)	2	(25)
	Pyrexia	2	(10)	3	(14)	0	
	Rigors	0		0		1	(13)
Musculoskeletal and connective tissue disorders	Back pain	0		1	(5)	0	
	Chest wall pain	1	(5)	0		0	
	Myalgia	0		0		1	(13)
Nervous system disorders	Dizziness	12	(57)	6	(29)	4	(50)[b]
	Headache	2	(10)	5	(24)	2	(25)
Respiratory, thoracic, and mediastinal disorders	Rales	17	(81)	10	(48)	6	(75)[c]
	Lung crackles	1	(5)	4	(19)	0	
	Pharyngolaryngeal pain	0		4	(19)	0	
	Cough	0		3	(14)	4	(50)
	Rhonchi	0		3	(14)	2	(25)
	Throat irritation	0		2	(10)	1	(13)
	Nasal congestion	0		1	(5)	1	(13)
	Wheezing	1	(5)	1	(5)	0	
	Dyspnea	0		1	(5)	0	
	Epistaxis	0		0		1	(13)
Reproductive system disorders	Dysmenorrhea	1	(5)	0		0	
	Genital pruritus (female)	0		1	(5)	0	
	Vaginal irritation	0		1	(5)	0	
Skin and subcutaneous disorders	Erythema	0		1	(5)	0	
	Pruritus	1	(5)	0		0	
	Rash, NOS	0		1	(5)	0	

[a] Except as noted, AEs reported for individual subjects treated at the 2000-mg dose were new-occurrence AEs, ie, they were not previously reported for the same subject when treated at a lower meropenem dose.

[b] Three of these subjects also had dizziness reported as an AE during treatment at the 500-mg dose.

[c] Each of these 6 subjects also had rales reported as an AE during treatment at either the 500-mg dose (n=5) or the 1000-mg dose (n=1).

MedDRA Medical dictionary for regulatory activities. NOS Not otherwise specified.

No clinically significant changes from baseline to Day 2 were seen for hematology, clinical chemistry, or urinalysis variables. No AEs were reported relative to clinical laboratory test results. No clinically significant changes in vital signs were identified; increased values in some subjects appeared related to BAL procedures.

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