Tissue Penetration of Meropenem in Patients Undergoing Gynecologic Surgery

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The purpose of this study was to assess the tissue-penetrating ability of a new β-lactam antibiotic, meropenem, in 64 patients undergoing elective gynecologic surgery. Patients received a single 500-mg dose intravenously before surgery. Plasma and tissue concentrations of meropenem were highest at ~1 hour, and good tissue penetration was seen in the variety of specimens evaluated. The median plasma concentration at ~1 hour was 13.3 μg/mL. The median fluid and tissue concentrations at ~1 hour were as follows: cervix, 8.5 μg/g; endometrium, 2.3 μg/g; fallopian tube, 1.9 μg/g; myometrium, 3.6 μg/g; ovary, 2.3 μg/g; and uterus, 2.3 μg/g. These tissue concentrations exceed the MICs of meropenem for 90% of typical pathogens associated with gynecologic infections. Meropenem readily penetrates gynecologic tissue. A single 500-mg dose provides adequate tissue concentrations for treatment of gynecologic infections caused by susceptible pathogens.

The development of new antibiotics is crucial to assure continued efficacy against common pathogens. In a recent commentary, Levy [1] reminded us that many organisms have developed resistance to multiple antibiotics in both community and hospital settings. Furthermore, antibiotics that continue to be effective often have undesirable side effects that can limit their usefulness.

Meropenem is a new β-lactam antibiotic and a member of the carbapenem class. Meropenem has been shown to be four times more stable against inactivation by the human renal enzyme dehydropeptidase-I [2] than imipenem; therefore, plasma concentrations of meropenem are adequate without the addition of an enzyme inhibitor such as cilastatin [3]. The in vitro activity of meropenem against aerobic and anaerobic organisms (including β-lactamase-producing *Neisseria gonorrhoeae* [MIC for 90% of strains (MIC_{90}) = 0.12 μg/mL]), Enterobacteriaceae species (MIC_{90} = 0.125 μg/mL), and many nonfermentative gram-negative rods has been demonstrated to be superior than those of imipenem and other β-lactam agents [4, 5]. The purpose of the current study was to evaluate the meropenem concentrations obtainable in gynecologic tissue, peritoneal fluid, and plasma after administration of a single intravenous 500-mg dose.

Methods

This multicenter, open-label trial evaluated hospitalized pre- or perimenopausal women who were older than 18 years of age, were not breast-feeding, weighed between 44 and 89 kg, and were scheduled to undergo elective gynecologic surgery. The Institutional Review Board at each center approved the study, and all patients gave written informed consent before enrollment. Meropenem, 500 mg per vial, was supplied by Zeneca Pharmaceuticals (Wilmington, DE). The contents of one vial were reconstituted with 10 mL of sterile water for injection and were further diluted to 100 mL with normal saline; meropenem was administered by intravenous infusion over 30 minutes within 1 hour of reconstitution, before the start of surgery.

Biological samples (tissue and peritoneal fluid) were obtained at one of the following four intervals after the start of meropenem infusion: ~1 hour (30 minutes to 1 hour and 30 minutes), ~2 hours (1 hour and 31 minutes to 3 hours), ~4 hours (3 hours and 1 minute to 5 hours), or ~6 hours (5 hours and 1 minute or longer). The type of biological sample varied with the type of surgical procedure performed. Plasma samples were obtained before the administration of meropenem, at the time that the first tissue or fluid sample was obtained, and frequently again after the last tissue or fluid sample was obtained. Biological and plasma samples were stored at −70°C to −80°C until they were analyzed.

Informed consent was obtained from the patients or their parents or guardians, and the guidelines for human experimentation of the U.S. Department of Health and Human Services and/or those of the authors' institutions were followed in the conduct of the clinical research.

Financial support: A portion of this work was supported by Zeneca Pharmaceuticals Group.

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Clinical Infectious Diseases 1997;24(Suppl 2):S178–80

1058–4838/97/2402–0046$02.00

Table 1. Meropenem concentrations in plasma and tissue samples from women undergoing gynecologic surgery.

Sample type	Time after dose (h:min)			
	0:30–1:30	1:31–3:00	3:01–5:00	⩾5:01
Plasma				
Median concentration in μg/mL (range)	13.3 (4.7–33.4)	4.5 (2.0–11.7)	0.8 (0.4–2.2)	0.6 (0.4–6.31)
No. of samples	31	27	13	8
Tissue				
Cervix				
Median concentration in μg/g (range)	8.5 (5.4–8.5)	3.4	NS	NS
No. of samples	2	1		
Endometrium				
Median concentration in μg/g (range)	2.3 (1.7–10.2)	1.4 (1.0–3.3)	NS	NS
No. of samples	7	5		
Fallopian tube				
Median concentration in μg/g (range)	1.9 (0.3–3.4)	0.8 (0.4–2.3)	3.5	0.5 (0.4–0.7)
No. of samples	9	5	1	2
Myometrium				
Median concentration in μg/g (range)	3.6 (0.4–8.1)	1.5 (0.5–2.1)	0.4	NS
No. of samples	15	9	1	
Ovary				
Median concentration in μg/g (range)	2.3 (0.8–4.8)	1.8 (0.6–5.0)	0.8 (0.3–1.7)	NS
No. of samples	8	6	4	
Uterus				
Median concentration in μg/g (range)	2.3 (1.6–5.1)	1.3 (1.2–1.9)	NS	NS
No. of samples	3	4		

NOTE. NS = no samples available.

Routine prophylactic antibiotics were not given until after all samples were obtained. Validated bioassay procedures were used to determine the meropenem concentrations in both plasma (detection limit, 0.25 μg/mL) and tissue samples (detection limit, ~1 μg/g). All data were summarized with use of the SAS system (SAS Institute, Cary, NC) and the RS 1 software package (BBN Software Products Corporation, Cambridge, MA).

Table 2. In vitro activity of meropenem against gynecologic pathogens.

Organism	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Neisseria gonorrhoeae		
β-Lactamase-negative	0.015	0.03
β-Lactamase-positive	0.015	0.50
Penicillin-resistant and β-lactamase-negative	0.03	0.03
Escherichia coli	0.03	0.03
Streptococcus agalactiae	0.06	0.06
Enterococcus faecalis	4	4
Bacteroides fragilis	0.125	0.25
Peptostreptococcus species	0.125	0.25

NOTE. Table adapted from [6]. MIC_{50} = MIC for 50% of strains; MIC_{90} = MIC for 90% of strains.

Results

Sixty-four patients (mean age ± SD, 38.4 ± 8.1 years; mean weight ± SD, 71.2 ± 13.9 kg; racial groups: black, 21 patients; white, 31; Oriental, 11; and other, 1) from four centers were enrolled in the trial. The pharmacokinetic data for five patients were excluded; one patient was withdrawn from the study because of chest pain before receiving meropenem, and four patients were withdrawn because of cancellation of surgery or incorrect sampling procedures.

Meropenem showed good penetration into a variety of gynecologic tissues (table 1). The median tissue concentrations averaged ~4 μg/g during the first interval (~1 hour) and decreased with increasing time. The median peak tissue concentrations in individual specimens at ~1 hour were 14.8% to 52.6% of the median plasma concentration at ~1 hour. At 30 minutes to 1 hour and 30 minutes, the ratio of the median individual tissue concentrations to the plasma concentration ranged from 1% to 64%; at 1 hour and 31 minutes to 3 hours, the ratio ranged from 18% to 76%.

The single sample of peritoneal fluid tested was obtained at ~1 hour; it contained 8.8 μg of meropenem/mL. Collection times for plasma and tissue samples after the start of infusion ranged from 5 minutes to ~7.5 hours and 45 minutes to ~7.25 hours, respectively. Samples taken before 30 minutes were not used in calculations of medians.

Nineteen patients (32%) had a total of 33 adverse events; none were considered by the investigators to be related to administration of meropenem. The most frequently reported adverse events (≥4 reports) were nausea (7) and pruritus (4).

Discussion

The current study demonstrates that meropenem is safe and well tolerated. A single 500-mg dose of meropenem provides adequate tissue concentrations in patients undergoing gynecologic surgery. The median peak tissue concentrations of meropenem at ~1 hour were 14.8% to 52.6% of the median plasma concentration at ~1 hour. The tissue concentrations were well above the MIC_{90} values for pathogens likely to be associated with gynecologic infections (table 2) [6]. The efficacy of meropenem as treatment for patients with gynecologic infections caused by susceptible organisms merits further evaluation.

Acknowledgments

The authors thank Phyllis Petryk and David Brooks for excellent technical assistance during the conduct of these investigations.

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