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Pharmacokinetic Profile of Meropenem, Administered at 500 Milligrams Every 8 Hours, in Plasma and Cantharidin-Induced Skin Blister Fluid

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The pharmacokinetic disposition of meropenem, administered at 500 mg every 8 h, in plasma and cantharidin-induced blister fluid is described. Peak meropenem concentrations in blister fluid lagged behind peak meropenem concentrations in plasma, while a lower elimination rate from blister fluid was also noted. The mean penetration of meropenem into blister fluid was 67%. The pharmacokinetic profile of meropenem in blister fluid supports the utility of this dose in the management of skin and soft tissue infections.

In the United States, meropenem is Food and Drug Administration approved for intra-abdominal infections and bacterial meningitis (Merrem package insert; AstraZeneca Pharmaceuticals, Wilmington, Del., 2001). However, this agent has also been found effective for lower respiratory tract, skin and soft tissue, gynecologic, and complicated urinary tract infections as well as empirical therapy in the febrile neutropenic patient (2–4, 6, 9, 11). While these clinical findings may be anticipated from its plasma profile, it is the drug concentration at the site of infection that best supports clinical efficacy. In the context of skin and soft tissue infections, evaluation of drug concentrations in blister fluid may best approximate drug exposure at the infection site, since this fluid has been noted to resemble the situation within an infected tissue (1). In this study, we evaluated the steady-state pharmacokinetic profile of meropenem, administered at 500 mg every 8 h, in both blister fluid and plasma.

Study design and population. Ten volunteers were enrolled in this multiple-dose, open-label study after approval was granted from the Hartford Hospital Institutional Review Board, and written informed consent was obtained. Volunteers were 21 to 42 years of age (mean age, 26.8 years), weighed between 68 and 118 kg (mean weight, 86.2 kg), and had a mean height of 1.8 m (range, 1.68 to 1.88 m). Volunteers underwent two complete physical exams within 21 days and 48 h before the study and were considered normal. Laboratory evaluations, including blood chemistries, hematology, and urinalysis, revealed no abnormalities.

Blister induction and drug administration. Volunteers received intravenous doses of 500 mg of meropenem (lot no. 6199C; AstraZeneca Pharmaceuticals) in 250 ml of normal saline over 30 min every 8 h for a total of three doses. After the first dose, and approximately 14 h before pharmacokinetic sampling, 0.2-ml drops of an ointment containing 0.25% cantharidin made from cantharidin powder (Sigma Laboratories, St. Louis, Mo.) and standard ointment base were applied to the anterior forearms of the volunteers to produce a total of six blisters per volunteer. The integrity of the blisters was maintained by spraying them with a fast-drying plastic dressing (New-Skin Liquid Bandage Spray; Medtech Laboratories, Inc., Jackson, Wyo.). Volunteers were allowed to take food and drink ad libitum. Caffeine intake was not permitted.

Pharmacokinetic sampling. Blood samples were collected into heparinized Vacutainers from an indwelling catheter contralateral to that used for drug administration just prior to (time 0) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 12 h after the start of the third infusion. Samples were kept on ice at all times and were centrifuged within 15 min at 2 to 8°C at 2,400 × *g* for 10 min. Simultaneously blister fluid samples (100 to 200 μl) were obtained. All samples were stored at −80°C until assayed. Samples were analyzed by a validated procedure in which the extraction of meropenem from plasma or blister fluid was accomplished by protein precipitation and detection by high-performance liquid chromatography–tandem mass spectrometry with a PE/SCIEX API 365 system with electron ionization. The method has a quantitation range of 0.50 to 50.0 μg/ml. Three quality control samples were used, and the mean coefficients of variation for the low (1.5 μg/ml), middle (15.0 μg/ml), and high (40.0 μg/ml) check samples were 5.5, 7.0, and 8.8%, respectively.

Pharmacokinetic parameters were derived individually for each subject. The maximum concentration of drug (meropenem) in serum (C_{max}) was obtained directly from the experimental data, with T_{max} (time to maximum concentration of drug in serum) defined as the time of the first occurrence of C_{max}. The elimination rate constant (k_{el}) was estimated by least-square regression analysis of plasma drug concentration-time data obtained during the terminal log-linear phase with WinNonlin 3.1 (Pharsight Corp., Mountain View, Calif.). A minimum of four data points were used to estimate the elimination rate constant. The elimination half-life ($t_{1/2}$) was cal-

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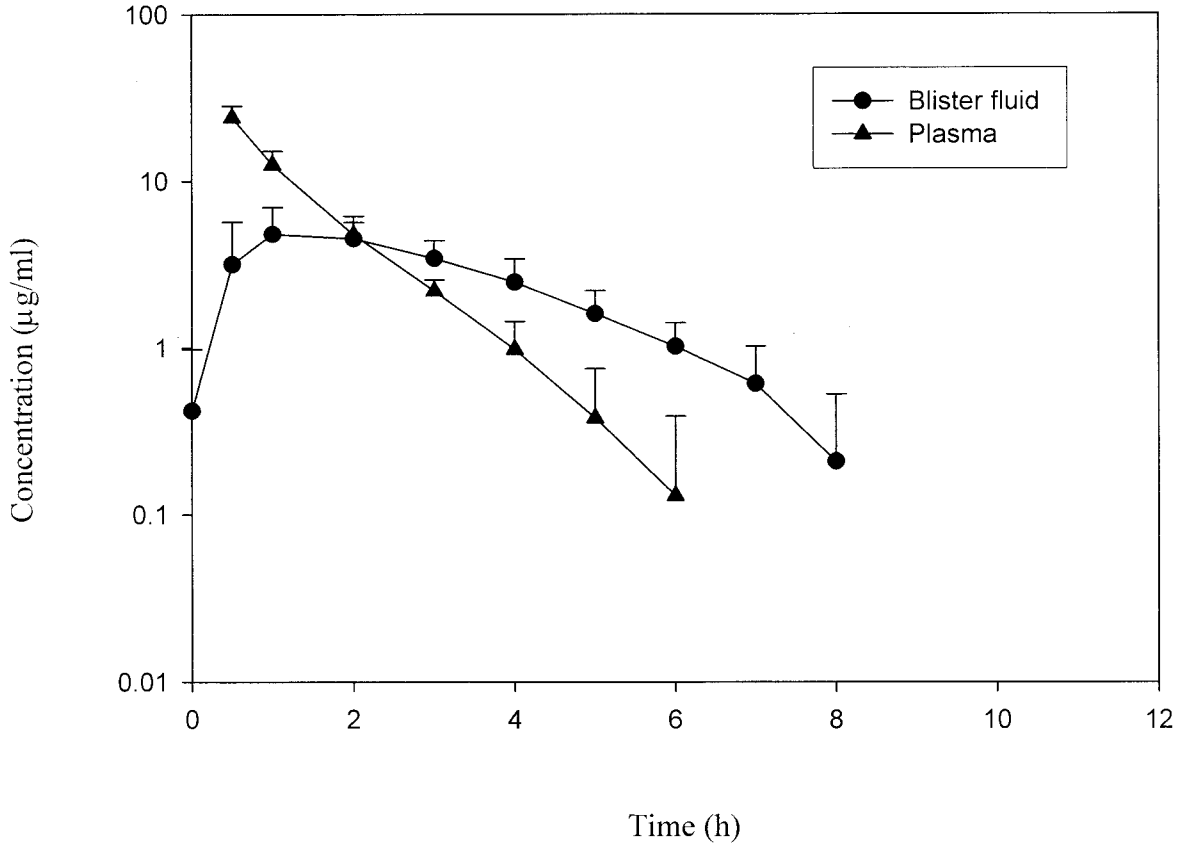

FIG. 1. Mean ± standard deviation steady-state meropenem concentrations in plasma and blister fluid versus time following a 30-min infusion of 500 mg every 8 h.

culated as $0.693/k_{el}$. The area under the concentration-time curve (AUC) was calculated by the linear trapezoidal rule method. The penetration of meropenem into blister fluid was determined by comparing the AUC from 0 to 8 h (AUC_{0-8}) in blister fluid with that in plasma.

Overall, meropenem was well tolerated. Two volunteers complained of headaches. Another experienced nausea and vomiting during the first two doses and was withdrawn. This event was considered possibly related to study medication; however, a virus causing similar symptoms had been prevalent in the local community during the time of the study. No significant changes in biochemical or hematological parameters were found. The concentration-versus-time profiles of plasma and blister fluid for nine volunteers are depicted in Fig. 1. The values are reflective of data obtained only from individuals who had measurable levels at each time point. Table 1 displays the individual pharmacokinetic data. The mean (± standard deviation) peak meopenem concentration in plasma was 24.02 ± 4.26 μg/ml. There was a log-linear decrease in the concentration of meropenem in plasma, with a mean elimination half-life

TABLE 1. Pharmacokinetic parameters of meropenem in plasma and blister fluid

Volunteer no.[a]	Plasma				Blister fluid			
	T_{max} (h)	C_{max} (μg/ml)	AUC_{0-8} (μg · h/ml)	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (μg/ml)	AUC_{0-8} (μg · h/ml)	$t_{1/2}$ (h)
1	0.50	22.20	23.49	0.73	1.08	6.83	20.31	2.10
2	0.50	28.60	33.11	1.46	0.58	8.58	31.36	1.41
3	0.50	23.10	29.81	0.88	0.57	4.70	16.49	1.62
4	0.53	19.70	26.74	1.19	1.07	4.54	11.57	1.45
5	0.50	21.40	25.07	1.00	2.02	3.21	13.63	2.47
6	0.52	32.80	39.18	0.90	2.02	4.39	18.14	2.21
7	0.55	25.70	27.38	0.74	1.07	7.98	21.75	1.64
9	0.53	21.00	26.51	1.01	2.03	5.48	19.96	1.92
10	0.50	21.70	26.23	0.71	0.58	3.60	17.03	1.68
Mean ± SD	0.50 ± 0.02	24.02 ± 4.26	28.61 ± 4.84	0.96 ± 0.25	1.22 ± 0.64	5.48 ± 1.91	18.92 ± 5.68	1.83 ± 0.36

[a] Volunteer no. 8 was withdrawn from the study as described in the text.

of 0.96 ± 0.25 h. At 7 h, the plasma meropenem concentration was undetectable in all participants. The mean AUC_{0-8} in plasma was 28.61 ± 4.84 μg · h/ml.

The T_{max} in blister fluid occurred at 1.22 ± 0.64 h. By 2 h, the meropenem concentrations in plasma and blister fluid were equivalent, and beyond 2 h, concentrations in blister fluid exceeded those in plasma. The apparent elimination half-life in blister fluid was 1.83 ± 0.36 h, as assessed until the 7th h. The terminal elimination rate was not calculated over the entire dosing interval, since values from only three participants remained above the detectable level at the 8-h sampling point. At 12 h, meropenem was undetectable in the blister fluid in all participants. The AUC_{0-8} ratio in blister fluid compared to that in plasma was calculated individually for each volunteer, and the mean percent penetration of meropenem into blister fluid was 67% ± 19%.

This study confirms that meropenem when given at 500 mg every 8 h penetrates well into skin blister fluid. The penetration and kinetics of meropenem in blister fluid have been investigated previously; however, the doses and methodologies used in these studies were different, a point that should be considered when making comparisons between studies. Mouton and colleagues (5) found the penetration into suction blister fluid to be 84.7% following a 10-mg/kg dose. Wise and colleagues (12) also investigated cantharidin-induced skin blisters; however, they utilized smaller blisters (1 cm^2 versus 1.6 cm^2). In this study, a single 1,000-mg meropenem dose was infused over 5 min, and the mean peak concentration in blister fluid occurred at 0.75 h. The percent penetration of meropenem into blister fluid in that study was 110%; however, when corrected for an extraordinarily high value in one volunteer, the percent penetration was 100.4%. A smaller blister size may explain the higher rate and larger percent penetration of meropenem observed by Wise due to differences in blister volume (7, 8).

Wise and colleagues (12) observed a half-life in blister fluid of 1.1 h, similar to that in serum, whereas our half-life in blister fluid was 1.83 h. This difference may be explained by the frequency of sampling from each blister. Wise et al. utilized two blisters per volunteer in their pharmacokinetic evaluation. This methodology results in the need for more frequent sampling from each blister. As a result, the drug profile in newly produced blister fluid may approximate the declining concentration of drug in plasma, whereas in the current study, we created six blisters per volunteer and each blister was entered into an average of less than two times. Since fluid was not extracted as frequently from each blister in the current study, the decline in concentration from this matrix was not influenced to the same degree by the declining concentration of meropenem in the central compartment.

Although certain differences were noted, our data support that meropenem penetrates well into inflammatory exudate, with concentrations exceeding those in plasma after 2 h when given at a dose of 500 mg every 8 h. These data also support the efficacy seen with this regimen as monotherapy in the treatment of skin and soft tissue infections (6). Blister fluid models aim to simulate an infected tissue compartment with similarities that include leukocyte and protein content. However, the dissimilarities as well as the likenesses should always be kept in mind when considering an experimental model in the context of a clinical situation. The model presented here would more closely approximate an infection site where exchange of drug is not rapid, such as an empyema, whereas a tissue thread model may simulate an infection site where a more rapid exchange of drug is expected (7). These differences may not be significant enough to predict success versus failure for the majority of pathogens associated with skin and soft tissue infections. However, for pathogens for which MICs approach the meropenem breakpoint of 4 μg/ml, the rate at which drug concentrations decline may be more important.

The pharmacodynamic parameter that correlates best with efficacy for β-lactams is the duration of time antibiotic concentrations exceed the MIC ($T>$MIC) (10). For the carbapenems, a 30% $T>$MIC has been suggested to optimize efficacy (R. Walker, D. Andes, J. Conklin, S. Ebert, and W. Craig, Abstr. 34th Intersci. Conf. Antimicrob. Agents Chemother., abstr. A91, 1994). For skin and soft tissue infections, the most common target pathogens are *Staphylococcus aureus* and *Streptococcus pyogenes*. Based our study, meropenem at 500 mg every 8 h maintained concentrations in blister fluid exceeding 4 and 17 times the meropenem MICs for methicillin-suseptible *S. aureus* (MIC at which 90% of the isolates tested are inhibited [MIC_{90}], 0.25 μg/ml) and *S. pyogenes* (MIC_{90}, < 0.06 μg/ml), respectively, for at least 70% of the dosing interval. Similarly, the meropenem concentrations obtained in blister fluid greatly exceeded the MIC_{90}s for other relevant pathogens, including *Escherichia coli* (<0.06 μg/ml), *Haemophilus influenzae* (0.13 μg/ml), *Clostridium perfringens* (0.06 μg/ml), and *Bacteroides fragilis* (0.5 μg/ml).

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REFERENCES

1. **Bergan, T., A. Engeset, W. Olszewski, N. Østby, and R. Solberg.** 1986. Extravascular penetration of highly protein-bound flucloxacillin. Antimicrob. Agents Chemother. **30:**729–732.
2. **Drusano, G. L., H. Lode, and J. R. Edwards.** 2000. Meropenem: clinical response in relation to in vitro susceptibility. Clin. Microbiol. Infect. **6:**185–194.
3. **Garau, J., J. Blanquer, L. Cobo, S. Corcia, M. Daguerre, F. J. de Latorre, C. Leon, F. Del Nogal, A. Net, and J. Rello.** 1997. Prospective, randomized, multicenter study of meropenem versus imipenem/cilastatin as empiric monotherapy in severe nosocomial infections. Eur. J. Clin. Microbiol. Infect. Dis. **16:**789–796.
4. **Hurst, M., and H. M. Lamb.** 2000. Meropenem: a review of its use in patients in intensive care. Drugs **59:**653–680.
5. **Mouton, J. W., and M. F. Michel.** 1991. Pharmacokinetics of meropenem in serum and suction blister fluid during continuous and intermittent infusion. J. Antimicrob. Chemother. **28:**911–918.
6. **Nichols, R. L., J. W. Smith, R. W. Geckler, and S. E. Wilson.** 1995. Meropenem versus imipenem/cilastatin in the treatment of hospitalized patients with skin and soft tissue infections. South. Med. J. **88:**397–404.
7. **Ryan, D. M., B. Hodges, G. R. Spencer, and S. M. Harding.** 1982. Simultaneous comparison of three methods for assessing ceftazidime penetration into extravascular fluid. Antimicrob. Agents Chemother. **22:**995–998.
8. **Shyu, W. C., R. Quintiliani, C. H. Nightingale, and M. N. Dudley.** 1988. Effect of protein binding on drug penetration into blister fluid. Antimicrob. Agents Chemother. **32:**128–130.
9. **Sieger, B., S. J. Berman, R. W. Geckler, and S. A. Farkas.** 1997. Empiric treatment of hospital-acquired lower respiratory tract infections with meropenem or ceftazidime with tobramycin: a randomized study. Crit. Care Med. **25:**1663–1670.
10. **Turnidge, J. D.** 1998. The pharmacodynamics of beta-lactams. Clin. Infect. Dis. **27:**10–22.
11. **Verwaest, C.** 2000. Meropenem versus imipenem/cilastatin as empirical monotherapy for serious bacterial infections in the intensive care unit. Clin. Microbiol. Infect. **6:**294–302.
12. **Wise, R., M. Logan, M. Cooper, J. P. Ashby, and J. M. Andrews.** 1990. Meropenem pharmacokinetics and penetration into an inflammatory exudate. Antimicrob. Agents Chemother. **34:**1515–1517.