

Meropenem Pharmacokinetics and Penetration into an Inflammatory Exudate

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The pharmacokinetics and penetration into a cantharidine-induced inflammatory exudate of meropenem was studied in six volunteers following a single 1-g intravenous dose. Concentrations in plasma, urine, and the inflammatory exudate were determined by a microbiological assay. The mean elimination half-life of meropenem in plasma was 1.1 h, with the concentration in plasma declining from a mean of 23.6 $\mu\text{g/ml}$ at 1 h to 0.7 $\mu\text{g/ml}$ at 6 h. The inflammatory fluid penetration was rapid (time to maximum concentration of drug in serum, 0.75 h), and the penetration was 111%. The recovery of meropenem in urine at 24 h was 65.4% of the administered dose.

Meropenem is a new carbapenem antimicrobial agent which shares with imipenem an α -hydroxyethyl at C-4 but differs in that it has a methyl group at C-1 and a dimethyl-carbamoylpyrrolidinethio side chain at C-3 (8). It is probable that the C-3 substituent accounts for the enhanced activity of this agent against gram-negative bacteria (3, 5). Of considerable importance is the fact that studies in animals suggest that meropenem is relatively more stable to hydrolysis by the renal dehydropeptidase I (DHP-I) (3) than imipenem, and preliminary studies in humans confirm this stability, suggesting that a DHP-I enzyme inhibitor such as cilastatin is not necessary (1). This property is probably associated with the methyl substituent at C-4, as other agents with this structure have been associated with enhanced resistance to DHP-I (13).

In this study we investigated the pharmacokinetics of meropenem in healthy volunteers, including the penetration of this agent into a chemically induced mild inflammatory exudate (14).

MATERIALS AND METHODS

Six healthy adult male volunteers participated after approval was received from the Ethical Committee of Dudley Road Hospital and written informed consent was obtained from the volunteers. They were aged 23 to 31 years (mean age, 23.6 years), weighed between 63 and 80 kg (mean weight, 69.9 kg), and had a mean height of 1.8 m (range, 1.69 to 1.87 m). The body weights were within 10% for their age and height. Medical history indicated no significant illness or allergies to β -lactam antibiotics. Hematological and biochemical profiles, including tests of renal and hepatic functions, were normal. One week prior to the study, all volunteers underwent a detailed physical examination and were considered normal. On the night before the study, two 0.2% cantharides-impregnated plasters (1 by 1 cm) were applied to the anterior surface of one forearm of each volunteer and taped in place. After overnight fasting, the subjects were given a single 1,000-mg intravenous injection (lot no. 6631; ICI Pharmaceuticals Ltd.) of meropenem sodium dissolved in 20 ml of water that was infused over 5 min. The volunteers were allowed to take solid food and drink after 2 h. Blood was drawn through an intravenous cannula (which was kept patent with 2-ml doses of heparinized saline [100 IU/ml])

immediately prior to infusion and then at 15, 30, 45, 60, and 90 min and 2, 3, 4, 5, 6, 8, and 12 h after dosing. Urine samples were collected from 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h after dosing. Inflammatory exudate from the blisters was sampled with a micropipette pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 12 h post-dose. The integrity of the blisters was maintained by spraying them with a fast-drying plastic dressing (Nobecutane; Astra Pharmaceuticals Ltd., Kings Langley, United Kingdom). Antibiotic assays were performed within 1 h of sample collection by the plate diffusion method. The plate diffusion assay indicator organism was *Escherichia coli* NIJH. The medium was Iso-Sensitest agar (pH 7.2; Oxoid, Ltd. Basingstoke, United Kingdom), which was incubated overnight at 37°C aerobically. Standards were prepared by using human serum for serum samples (pooled human serum; Flow Laboratories, Irvine, United Kingdom) and 70% human serum in phosphate buffer (pH 7) for blister inflammatory exudates. Urine samples were diluted and prepared in phosphate buffer (pH 7). Results were calculated by using the correction of Bennett et al. (2) to give a line of best fit for the standard curve. The lower limit of sensitivity of the assay was 0.1 $\mu\text{g/ml}$. Three internal controls were used; and the mean coefficients of variation of the assay between days were 6.3% at 0.4 $\mu\text{g/ml}$, 6.8% at 3.0 $\mu\text{g/ml}$, and 5.9% at 20 $\mu\text{g/ml}$.

Pharmacokinetic analysis of meropenem in serum was performed with the GPHARM program (4) by assuming a two-compartment model using the computational algorithm of peeling, with seven to eight points being fitted to the elimination phase. The structural model assumed a bolus injection. No corrections were applied for the 5-min infusion. Pharmacokinetic parameters for the inflammatory fluid were determined by standard graphical methods of individual volunteer data (12). This included the area under the concentration-time curve (AUC), which was calculated by a log-linear trapezoidal rule procedure. The percent penetration of meropenem into inflammatory exudate was calculated by comparing the AUC from 0 h to infinity ($\text{AUC}_{0-\infty}$) in inflammatory exudate with that in serum.

RESULTS

Figure 1 depicts the levels of meropenem in plasma and inflammatory fluid following the 1,000-mg bolus injection, and Table 1 shows the derived pharmacokinetic data. The

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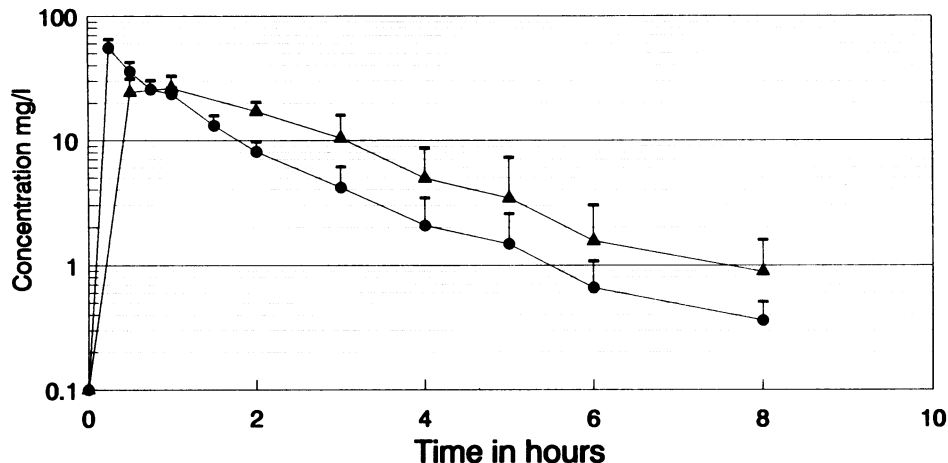


FIG. 1. Levels of meropenem in serum (●) and inflammatory fluid (▲) following administration of 1,000 mg of meropenem intravenously to six volunteers. Bars indicate standard deviations.

mean concentration in plasma at 0.25 h postdose was 55.6 $\mu\text{g/ml}$ (range, 43.7 to 66.5 $\mu\text{g/ml}$). Inspection of the pharmacokinetic profiles from the individual volunteers suggested that the distribution of meropenem was essentially complete by 1 h postdose, when the mean level in plasma was 23.6 $\mu\text{g/ml}$ (range, 19.6 to 26.9 $\mu\text{g/ml}$). Thereafter, there was a log-linear decline in the concentration in plasma with time to a mean of 0.7 $\mu\text{g/ml}$ (range, 0.3 to 1.3 $\mu\text{g/ml}$) at 6 h. At 12 h the levels had fallen below the lower limit of sensitivity of the assay for all volunteers. The mean plasma elimination half-life of meropenem was 1.1 h, with a range of 0.9 to 1.4 h.

Penetration of meropenem into the inflammatory exudate was rapid, with the mean concentration at 0.5 h being 24.2 $\mu\text{g/ml}$ (range, 11.9 to 29.3 $\mu\text{g/ml}$), and the mean peak concentration was 28.3 $\mu\text{g/ml}$ (range, 22.6 to 37.4 $\mu\text{g/ml}$) and was attained at 0.5 h in three volunteers and 1.0 h in the remaining three volunteers. The mean elimination half-life from the inflammatory exudate was 1.1 h. The mean percent

penetration of the inflammatory exudate (calculated from individual ratios of $\text{AUC}_{0-\infty}$ for inflammatory fluid and $\text{AUC}_{0-\infty}$ for plasma) was 110.7% (range, 88.0 to 130.4%). In all volunteers, the inflammatory exudate levels exceeded those in plasma by 1 h, and by 6 h the mean level in inflammatory exudate was 1.5 $\mu\text{g/ml}$ (range, 0.14 to 2.13 $\mu\text{g/ml}$). The mean volume of distribution of meropenem at steady state was 20.6 liters.

The mean recovery of meropenem from the urine at 24 h was 65.4% (range, 52.0 to 73.0%) of the administered dose, with 62.3% being eliminated in the first 4 h. The mean total clearance of meropenem from the body was 253 ml/min (range, 208 to 329 ml/min), and the mean renal clearance was 182 ml/min (range, 131 to 241 ml/min).

Other than one volunteer with a headache, no adverse effects of meropenem were experienced by the volunteers and no alterations to biochemical or hematological parameters were found.

DISCUSSION

The pharmacokinetics of meropenem are broadly in agreement with those presented previously (1), with the exception that the recovery in urine reported by Bax et al. (1) was a mean of 79%, in comparison with that in this study, which was a mean of 65.39%. It is possible that because the agent is excreted rapidly, leading to very high levels in urine in the sample from 0 to 4 h postdose, there must be large dilutional factors necessary to perform the assay. Minor inaccuracies in such steps could lead to considerable errors. The assay itself is unlikely to be a source of error, as the $\text{AUC}_{0-\infty}$ for plasma that we obtained was exactly that reported by Bax et al. (1).

There appear to be two major differences in the pharmacokinetics of meropenem and imipenem. The first is the higher urinary recovery of meropenem. In a similar study (with a different volunteer group) following a 500-mg injection of imipenem, a mean urinary recovery of 14.7% was found, which increased to 55.6% when imipenem was coadministered with an equal amount of cilastatin (7). Hence, the recovery of meropenem exceeds that of imipenem even without the use of a DHP-I inhibitor. The second difference appears to be a possibly greater ability of meropenem, compared with that of imipenem, to penetrate tissues. By a similar method of analysis, the percent penetration of imi-

TABLE 1. Pharmacokinetics of meropenem in six healthy volunteers

Parameter in the indicated fluid ^a	Mean \pm SD	Range
Plasma		
$t_{1/2\beta}$ (h)	1.1 \pm 0.2	0.9–1.4
$\text{AUC}_{0-\infty}$ ($\mu\text{g} \cdot \text{h/ml}$)	66.9 \pm 13.7	50.6–80.1
CL_T (ml/min)	253 \pm 51.5	208–303
CL_R (ml/min)	181.8 \pm 46.5	130.5–240.5
V_{ss} (liter)	20.6 \pm 5.9	15.1–21.6
Inflammatory exudate		
C_{max} ($\mu\text{g/ml}$)	28.3 \pm 5.0	22.6–37.4
T_{max} (h)	0.75 \pm 0.3	0.5–1.0
$t_{1/2\beta}$ (h)	1.1 \pm 0.4	0.6–1.6
$\text{AUC}_{0-\infty}$ (mg \cdot h/ml)	73.4 \pm 16.1	54.6–93.7
% Penetration ^b	111 \pm 15.6	88–130
Urine recovery (% of dose)		
0–4 h	62.3 \pm 8.9	49.8–70.8
0–24 h	65.4 \pm 8.8	52.0–73.1

^a Abbreviations: $t_{1/2\beta}$, half-life at the elimination (β) phase; $\text{AUC}_{0-\infty}$, AUC from 0 h to infinity; CL_T , total clearance; CL_R , renal clearance; V_{ss} , volume of distribution at steady state; C_{max} , mean peak concentration; T_{max} , time to maximum concentration of drug in serum.

^b $\text{AUC}_{0-\infty}$ inflammatory fluid \times 100/ $\text{AUC}_{0-\infty}$ plasma.

penem into inflammatory fluid was $67.8 \pm 13.8\%$ (standard deviation) when given with inhibitor and $73.2 \pm 13.9\%$ (standard deviation) when given alone (7). The penetration of meropenem was $110.0 \pm 15.6\%$ (standard deviation). Meropenem also compares favorably in this respect when it is compared with cefepime (penetration, 80.4%) (10) and the penem FCE 22101 (penetration, 60.9%) (11). However, crossover studies should be performed to confirm these findings. The suggestion that meropenem penetrates tissue efficiently is further supported by the finding that the volume of distribution of this compound (20.6 liters) is greater than those of other β -lactams, for example, cefepime (13.6 liters) (10), FCE 22101 (16.6 liters) (11), and imipenem (16.7 liters) (as calculated from the data of Norrby et al. [9]). However, it is possible that the high degree of penetration reported here for meropenem might be an overestimate related to one outlier result of 130.4%. If this result were ignored, the mean percent penetration would be 100.4%.

The rapidity of penetration of meropenem into inflammatory fluid is also noteworthy, in that maximum levels were attained by 0.5 h in one-half of the volunteers and by 1 h in all volunteers. In this respect meropenem resembles imipenem (7).

Meropenem has a high level of activity against a wide range of bacterial pathogens. Members of the family *Enterobacteriaceae*, *Staphylococcus* spp. (other than methicillin-resistant strains), and *Bacteroides fragilis* are inhibited by low concentrations (MIC for 90% of strains, $\leq 0.25 \mu\text{g/ml}$) (6). These results therefore suggest that a twice-daily dosing of 1 g might be sufficient to treat these pathogens. *Pseudomonas aeruginosa* (MIC for 90% of strains, $4 \mu\text{g/ml}$) might require a larger dose or more frequent dosing. Clinical trials to support these observations are warranted.

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