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Note

Pharmacokinetics of Meropenem in Patients with Cystic Fibrosis

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Abstract The pharmacokinetics of meropenem were studied after single i.v. infusions of 15 mg meropenem/kg body weight in eight subjects with cystic fibrosis (CF) and eight healthy volunteers matched for age, sex, and weight. Significantly shorter terminal half-lives (mean, 0.74 h vs. 0.99 h) and mean residence times (mean, 1.09 h vs. 1.39 h) were noted in CF subjects. Plasma and renal clearances tended to be higher and distribution volumes smaller among the patients, but differences were not statistically significant. The results are consistent with the findings for many other beta-lactam agents used in CF patients. Assuming a MIC90 of 4 mg/l for meropenem against *Pseudomonas aeruginosa*, the time above the MIC was less than 3.3 h in six of the eight CF patients. This finding should be kept in mind when designing treatment regimens with meropenem in CF subjects.

Introduction

Meropenem is a carbapenem antibiotic that is relatively stable against renal dehydropeptidase. It has a broad spectrum of activity against gram-positive and gram-negative aerobic and anaerobic bacteria. It is two to four times more active than imipenem against *Pseudomonas aeruginosa* and *Burkholderia cepacia* [1, 2]. Meropenem should therefore be useful in treating exacerbations of cystic fibrosis (CF) [3].

The disposition of many antibiotics is altered in CF patients [4–6]. We investigated the single-dose pharmacokinetics of meropenem in CF patients in stable clinical condition and in healthy volunteers.

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Materials and Methods

The study protocol was approved by the Research Ethics Committee of the Medical Faculty, University of Lund, and by the Swedish Medical Products Agency. All subjects gave written informed consent before entering the study.

Eight patients with CF and eight healthy volunteers matched for sex, age, and weight were included. Table 1 shows the demographic data for both groups. All CF patients had been diagnosed in infancy or early childhood. The vital capacities and forced expiratory volumes during 1 s (FEV_1) are presented as markers for severity of disease. All CF patients had clinically significant lung disease and pancreatic insufficiency, and two had diabetes. They were in stable condition without acute infection and had received no antibiotics during the previous 4 weeks. Control subjects had not received any regular drug treatment during the 3 months preceding the study. No subjects were tobacco users.

Screening tests performed before the study began included an electrocardiogram and a test for hepatitis B surface antigen. Laboratory tests were performed before infusion began and 24 and 48–96 h after infusion; they consisted of a complete hematology screen and determination of serum liver enzymes, bilirubin, creatinine, and albumin. Glomerular filtration rate was assessed by iohexol clearance determination [7] on the study day. A complete clinical examination was done at the time of the pre-study screening.

On the study day, subjects were given a light breakfast before dosing and were allowed to drink freely but had no food for 3 h after start of infusion. Blood pressure and pulse rate were recorded before dosing and 15 min and 3 h after the start of infusion. Subjects were actively questioned regarding symptoms or possible side effects before, during, and after dosing. All observed events were recorded.

Meropenem (Zeneca Pharmaceuticals, UK) (1500 mg) was mixed with sodium carbonate (1:0.75 molar ratio) and diluted with 30 ml of sterile water; this mixture was immediately further diluted with 150 ml of sterile physiological saline less than 90 min before infusion. This solution was stored at +4 °C until used. After filling infusion lines and saving an aliquot for drug assay, a dose of 15 mg/kg was infused intravenously over 30 min by an infusion pump (B. Braun Perfusor ED 2; B. Braun, Melsungen, Germany). Blood samples were drawn from the contralateral arm before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h after the

start of infusion. Samples were centrifuged at +4 °C within 15 min, and plasma was rapidly frozen in an ethanol/dry ice mixture and stored at –70 °C until assayed. Urine was collected before and at 0–2, 2–4, 4–6, and 6–8 h after the start of infusion. The volume of each fraction was measured and an aliquot frozen as described above.

Results were calculated as the group mean, with one standard deviation and range as estimates of variability. Differences between groups were evaluated with the two-tailed Wilcoxon's rank sum test for unpaired observations. Significance was defined as a P value less than 0.05.

Concentrations of meropenem in infusion fluid, plasma, and urine were assayed by a previously described method employing high-performance liquid chromatography [8]. The limits of detection were 0.4 mg/l in plasma and 4 mg/l in urine. Inter- and intra-assay coefficients of variation were less than 6%.

The pharmacokinetic data were derived from plasma and urine concentration data using noncompartmental methods. The slope (λ_z) of the terminal linear phase of the semilogarithmic plasma concentration versus time curve was estimated by least-squares regression analysis. The area under the concentration curve extrapolated to infinity (AUC) was calculated by the trapezoidal rule during infusion and by the log trapezoidal rule after the end of infusion, with the residual area to infinite time determined by dividing the last measured concentration in serum by λ_z. The area under the first moment of the plasma concentration curve (AUMC) was obtained by the trapezoidal rule from the plot of the product of time and drug concentration versus time and extrapolated to infinity by the formula $(c_z \times t_z)/\lambda_z + (c_z/\lambda_z)^2$, where c_z is the plasma concentration at the last sampling time (t_z). The terminal half-life ($t1/2_{\lambda z}$) was determined as the ratio between ln2 and λ_z. The mean residence time was calculated as AUMC/AUC. Total plasma clearance (CL_T) was calculated as dose/AUC and corrected to 1.73 m^2 body surface area. Renal clearance (CL_R) was determined as the ratio of the amount of compound excreted into the urine during the 8 h sampling period to the area under the curve for the same period and corrected for body surface area. Subtraction of CL_R from CL_T yielded the nonrenal clearance (CL_{NR}). The apparent volume of distribution atsteady state (V_{ss}) was calculated as $(\text{dose} \times \text{AUMC}/\text{AUC}^2) - (\text{dose} \times T)/(2 \times \text{AUC})$, where T is the duration of infusion. Net tubular secretion was defined as CL_R-GFR.

Results and Discussion

The single doses of meropenem were well tolerated in all subjects, and no adverse events were noted. No significant changes were detected in laboratory values. The two groups were well matched with regard to sex, size, and age (Table 1).

No differences were observed in distribution volumes. Both CF subjects and healthy volunteers reached high and similar peak concentrations at the end of infusion, but plasma concentrations fell more rapidly in CF subjects, as demonstrated by a shorter $t1/2_{\lambda z}$ and mean residence time. We found no statistically significant differences in clearances. The pharmacokinetic variables of meropenem are summarised in Table 2. Due to incomplete urine collection, two subjects (1 in each group) had to be excluded from calculation of CL_R and hence CL_{NR}.

In 1975 it was observed that the pharmacokinetics of cloxacillin were altered in patients with CF as compared with healthy volunteers [5]. Since then, numerous antibiotics have been investigated and altered pharmacokinetics described for aminoglycosides, quinolones, and several beta-lactam antibiotics [4, 6, 9]. In two studies of imipenem-cilastatin [10, 11], it was concluded that the pharmacokinetics were unaffected by CF. However, these two studies did not include healthy controls.

In our investigation of meropenem, we noted a significantly shorter $t1/2_{\lambda z}$ and mean residence time in the CF patients. There was a tendency towards more rapid clearances and smaller volumes of distribution, but statistical significance was not achieved, mainly because of large inter-individual differences in both CF patients and controls. There is evidence that healthy volunteers are bimodally distributed regarding capacity to metabolise imipenem and meropenem by dehydropeptidase I [8]. Our results, which show smaller differences between groups in nonrenal than in total and in renal clearances, indicate that there are high and low metabolisers among our volunteers, both CF subjects and healthy controls.

Renal clearances of meropenem were greater than the glomerular filtration rate in both groups, indicating

Table 1 Demographic data of cystic fibrosis (CF) patients and healthy volunteers

Characteristic	Mean ± SD (range)	
	CF patients	Volunteers
Male : female ratio	6:2	6:2
Age in years	24 ± 4 (19–31)	25 ± 5 (20–34)
Weight in kg	62 ± 8.0 (54–76)	65 ± 6.0 (57–77)
BSA in m^2	1.72 ± 0.149	1.80 ± 0.104
GFR[a] in ml/min × 1.73 m^2	118 ± 12.4	105 ± 21.1
S-creatinine in μmol/ml	73 ± 14.3	78 ± 9.5
Percent of anticipated VC	83 ± 24 (48–108)	
Percent of anticipated FEV_1	60 ± 29 (25–109)	

[a] One CF patient excluded, no data available

BSA, body surface area; FEV_1, forced expiratory volumes during 1 sec; GFR, glomerular filtration rate; S-creatinine, serum creatinine; VC, vital capacity

Table 2 Single-dose intravenous pharmacokinetics of meropenem in cystic fibrosis (CF) patients and healthy volunteers

Pharmacokinetic data	Mean ± SD		
	CF patients	Volunteers	*P* value
Dose (mg)	1049 ± 116.0	1015 ± 72.3	
Cmax (mg/l)	79.4 ± 19.7	74.7 ± 14.7	0.63
AUC (h × mg/l)	82.1 ± 18.4	92.7 ± 22.1	0.40
λz (h^{-1})	0.97 ± 0.172	0.72 ± 0.145	0.005
$t1/2_{\lambda Z}$ (h)	0.74	0.99	NA
MRT (h)	1.09 ± 0.132	1.39 ± 0.174	0.007
V_{SS} (l)	11.0 ± 2.6	12.9 ± 2.3	0.16
CL_T (ml/(min × 1.73 m^2))	224 ± 58.3	185 ± 50.2	0.17
CL_R (ml/(min × 1.73 m^2))[a]	152 ± 50.1	127 ± 43.6	0.22
CL_{NR} (ml/(min × 1.73 m^2))[a]	70 ± 17.6	56 ± 28.9	0.34
U_{REC} (% of dose)[b]	70 ± 5.9	70 ± 14.2	0.75
Net tubular secretion (ml/min)[b]	18 ± 28	22 ± 27	0.89
Time to S-conc. 4 mg/l (h)	3.2 ± 0.52	3.9 ± 0.70	0.07

[a] One individual in each group excluded due to incomplete urine collection

[b] One individual in each group excluded due to incomplete urine collection; one CF patient excluded since GFR was not available

C_{max}, maximal serum concentration; AUC, area under concentration curve; λ_z, slope of terminal linear phase; MRT, mean residence time; V_{SS}, volume of distribution at steady state; $t1/2_{\lambda z}$, terminal half-life; CL_T, total plasma clearance; CL_R, renal clearance; CL_{NR}, nonrenal clearance; U_{REC}, urinary recovery; time to S-conc. 4 mg/l, time after dose when serum concentrations were >4 mg/l

active tubular secretion of the drug. The net tubular secretion was comparable in CF patients and in controls. It has been shown that subjects with CF have more acidic urine than healthy volunteers [9], which would decrease the degree of ionisation of a weak acid in urine and increase tubular absorption.

Another mode of reabsorption of weak acids proposed in CF subjects is a carrier-mediated transport mechanism in the renal tubule involving chloride and hydroxyl ions [12]. Chloride impermeability, the basic defect in CF, is expressed not only in the respiratory mucosa but also in other organ systems, such as the kidneys [13]. This finding implies, theoretically, that renal reabsorption of organic anions is decreased, which may explain the increased renal clearances often found for beta-lactam agents in CF patients. Although our study is small and the pH in urine was not measured, the two counteracting mechanisms may explain why no statistically significant differences were detected with regard to renal clearance and net tubular secretion of meropenem.

The variation in renal drug excretion among CF patients may, to a certain extent, be explained by changes in eliminatory capacity related to the severity of disease. A higher glomerular filtration rate has been noted in CF subjects with essential fatty acid deficiency [14]. It is important to bear in mind that our patients were examined between exacerbations of pulmonary infection and that no certain conclusions can be drawn regarding the kinetics during acute lung infection. Nevertheless, the kinetic changes found in our study are consistent with those observed for several other beta-lactam antibiotics [6].

The MIC90 of meropenem for *Pseudomonas aeruginosa* varies in different studies from 1 to 4 mg/l [1, 2]. The time plasma concentrations stay above the MIC appears to be an important determinant for clinical efficacy of beta-lactam agents [15]. Assuming an MIC90 of 4 mg/l, the times above the MIC were lower in several of our CF subjects (range, 2.1–3.9 h) compared with controls, being less than 3.3 h in six CF subjects. The mean value, however, was not significantly lower ($P = 0.07$). The rapid decline in meropenem concentrations in some CF subjects might require shorter dosing intervals in this patient group. Clinical trials are needed to establish the therapeutic efficacy of such dosage regimens.

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