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Pharmacokinetics of Meropenem and Its Metabolite in Young and Elderly Healthy Men

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The pharmacokinetics of meropenem and its ring-opened metabolite (ICI 213,689) were investigated with eight young (20- to 34-year-old) and eight elderly (67- to 80-year-old) healthy male volunteers given single 30-min intravenous infusions of 500 mg of meropenem. All subjects had normal age-correlated glomerular function. The mean terminal half-life of meropenem was 1.27 h in the elderly subjects versus 0.81 h in the younger subjects ($P < 0.001$). This and similar increases in mean residence time and area under the concentration-time curve were explained by a reduction in total [139 versus 203 ml/(min · 1.73 m^2); $P < 0.001$], renal, and nonrenal clearances in subjects at advanced ages. The apparent volume of distribution and urinary recovery over 8 h were not significantly altered. With the metabolite, prolonged serum half-life and mean residence time, enlarged area under the concentration-time curve, and lower renal clearance but no significant changes in peak plasma concentration or urinary recovery were found in the elderly. The reduction in the renal excretion rate of meropenem and its metabolite corresponds to the age-associated physiological decline in renal function. The capacity to metabolize meropenem may also be slightly impaired in people at advanced ages. Dose reduction of meropenem should be considered for elderly patients.

Meropenem (ICI 194,660), a new parenteral carbapenem antibiotic, is highly active against a broad spectrum of pathogenic bacteria (11). The compound is water-soluble and is eliminated mainly by renal excretion, through both glomerular filtration and tubular secretion (2, 16). In healthy volunteers, approximately 70% of the dose is recovered unchanged in urine, while most of the remainder is excreted as a ring-opened metabolite (ICI 213,689) (2, 10, 16). Since meropenem is more stable than imipenem against renal dehydropeptidase-1, it is not necessary to coadminister a renal dehydropeptidase-1 inhibitor in order to achieve high concentrations in urine (2, 10).

Advancing age is accompanied by a number of physiological changes with possible or proven impact on the kinetics of antibiotics (13). Because of its extended antibacterial spectrum and suitability for treatment of severe infections, meropenem may often be used in elderly subjects. In order to determine the impact of advanced age as such on the disposition of meropenem, we studied meropenem's pharmacokinetics in connection with single intravenous (i.v.) doses in eight young and eight elderly healthy volunteers.

(This study was presented in part at the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill., 29 September to 2 October 1991 [15a].)

MATERIALS AND METHODS

The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Lund University, Lund, Sweden, and by the Swedish Medical Products Agency.

Subjects. After giving informed consent, eight young (20- to 34-year-old) and eight elderly (67- to 80-year-old) male, nonsmoking volunteers were included in the study. Their basic characteristics are displayed in Table 1. None of the subjects had a history of renal or hepatic disorder or other serious disease, and none had experienced any acute illness within 1 week preceding the study. All volunteers were judged healthy at a prestudy clinical examination that included a laboratory screening. None was undergoing concurrent drug treatment. The consumption of coffee, tea, and alcohol-containing beverages was not permitted for 12 h before the pharmacokinetic study period or during the study period. Volunteers were confined to bed for the first 2 h following the start of infusion; during the remainder of the investigation, they were ambulatory.

Laboratory screening. The following laboratory tests were

TABLE 1. Basic characteristics[a] of the volunteers

Group (*n*)	Age (yr)[b]	Wt (kg)	Body surface area (m^2)	GFR [ml/(min · 1.73 m^2)][b,c]	Serum creatinine (μmol/liter)
Elderly (8)	73 ± 4.6	68.9 ± 8.3	1.81 ± 0.11	71.9 ± 12.0	89 ± 14.2
Young (8)	28 ± 5.2	68.6 ± 7.7	1.88 ± 0.15	99.3 ± 7.3	87 ± 8.0

[a] Group means ± SD.
[b] $P < 0.001$ (Wilcoxon's two-tailed rank sum test for unpaired observations).
[c] Iohexol clearance.

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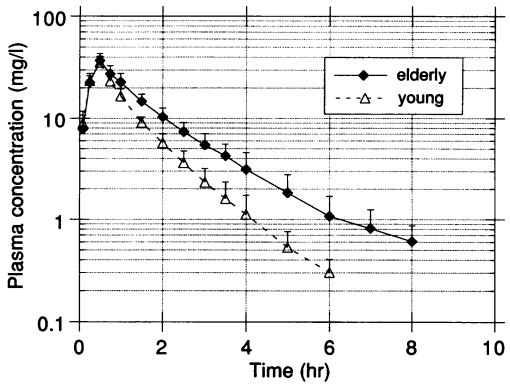

FIG. 1. Mean plasma concentrations (with SD) of meropenem in eight young and eight elderly healthy men following a 30-min i.v. infusion of 0.5 g of meropenem.

performed as part of the pretrial medical examination, before drug administration, and 24 and 48 to 96 h after infusion: hemoglobin concentration; packed erythrocyte volume; total and differential leukocyte counts; platelet count; erythrocyte sedimentation rate; urinalysis (pH, protein, glucose, blood, and microscopy); blood glucose, serum sodium, potassium, creatinine, urea, albumin, and bilirubin concentrations; and alkaline phosphatase, gamma-glutamyltransferase, and alanine and aspartate transferase activities.

The glomerular filtration rate (GFR) was determined by iohexol clearance (12) on the pharmacokinetic study day. All subjects had normal age-related GFRs according to the existing reference values based on inulin clearance, ^{51}Cr-EDTA clearance (9), and iohexol clearance (1).

Administration. Each volunteer received a single i.v. infusion of 500 mg of meropenem (ICI, Macclesfield, United Kingdom) over 30 min in the antecubital vein. The solution for infusion was prepared by dissolution of 1,000 mg of meropenem (meropenem trihydrate with sodium carbonate; the dose is given as the equivalent of anhydrous meropenem) in 20 ml of sterile water and by further dilution with sterile physiological saline to a total volume of 100 ml no more than 30 min before start of administration. Fifty milliliters of the final solution was administered; the excess solution was used to fill infusion lines and to save an aliquot for drug assay.

Sampling. Venous blood samples were drawn through an indwelling catheter in the contralateral arm before and 5, 15, 30, and 45 min and 1, 1½, 2, 2½, 3, 3½, 4, 5, 6, 7, and 8 h after the start of infusion. Urine was collected quantitatively over 0 to 2, 2 to 4, 4 to 6, and 6 to 8 h after the start of infusion. Blood samples were centrifuged at 4°C within 15 min. Two aliquots each of plasma and urine from each sampling time were rapidly frozen in a mixture of ethanol and dry ice and stored at −70°C until assayed for meropenem and metabolite. Aliquots of each infusion solution were collected and treated in a manner identical to that used for the plasma and urine samples.

Assays. Concentrations of meropenem in plasma and urine were determined by a previously developed method employing high-performance liquid chromatography (10, 16). The intra- and interassay imprecision (coefficient of variation) was below 6% for both serum and urine analysis, and the lower detection limits were 0.2 mg/liter in plasma and 2 mg/liter in urine. Concentrations of the metabolite, ICI 213,689, were analyzed by a radioimmunoassay at ICI Pharmaceuticals (3, 10). This assay had a sensitivity of 0.075 mg/liter, and the interassay coefficient of variation was below 15%.

Pharmacokinetic analysis. Noncompartmental analysis was used for pharmacokinetic calculations (8). The slope (λ_z) of the terminal linear phase of the plasma concentration-time curve was estimated by least-squares regression analysis. The area under the curve extrapolated to infinity (AUC) was calculated by the trapezoidal rule during infusion and by the log-trapezoidal rule after the end of infusion. The residual area to infinite time was determined from the quotient of the last measured plasma concentration and λ_z. The area under the first moment of the concentration-time curve (AUMC) was obtained by the log-trapezoidal rule from the plot of the product of time and drug concentration versus time and extrapolated to infinity by the formula $[(c_z \cdot t_z)/\lambda_z] + [c_z/(\lambda_z)^2]$, where c_z is the plasma concentration at the last sampling time (t_z). The terminal half-life ($t_{1/2\lambda_z}$) was determined by dividing ln2 by λ_z. The mean residence time (MRT) was calculated as AUMC/AUC.

Total serum clearance (CL_T) was calculated as dose/AUC. Renal clearance (CL_R) was determined as the ratio of the amount of compound excreted into the urine during 8 h to the area under the plasma concentration-time curve for the same time period. Subtraction of CL_R from CL_T yielded the nonrenal clearance (CL_{NR}). The apparent volume of distribution at steady state was given as $[(\text{dose} \cdot \text{AUMC})/\text{AUC}^2] - [(\text{dose} \cdot T)/(2 \cdot \text{AUC})]$, where T is the duration of injection. Clearances and steady-state volume of distribution were corrected to 1.73 m^2 of body surface area.

TABLE 2. Pharmacokinetic variables[a] for i.v. infusion of 0.5 g of meropenem over 30 min

Group[b]	C_{max} (mg/liter)[c]	λ_z (h^{-1})[d]	$t_{1/2\lambda_z}$ (h)[d]	MRT (h)[d]	AUC (h · mg/liter)[e]	Dose-corrected AUC (h · mg/liter)[e,f]	Clearance [ml/(min · 173 m^2)]			V_{55} (liters/1.73 m^2)[h]	Urinary recovery over 8 h (%)
							CL_T[d]	CL_R[e]	CL_{NR}[g]		
Elderly	37.0 ± 6.2	0.548 ± 0.076	1.27	1.85 ± 0.29	58.3 ± 10.0	58.4 ± 9.9	139 ± 20.0	99 ± 13.3[i]	39 ± 14.5[i]	13.2 ± 1.4	67.3 ± 4.7[i]
Young	35.6 ± 5.2	0.860 ± 0.099	0.81	1.22 ± 0.12	39.6 ± 6.8	38.7 ± 7.0	203 ± 28.4	137 ± 25.1	66 ± 17.5	11.7 ± 1.2	68.2 ± 7.9

[a] Group means ± SD.
[b] Statistical significance for comparisons between groups was determined by Wilcoxon's two-tailed rank sum test for unpaired observations.
[c] C_{max}, maximum concentration of drug in serum.
[d] $P < 0.001$.
[e] $P < 0.01$.
[f] Calculated for a dose of 500 mg.
[g] $P = 0.011$.
[h] V_{ss}, volume of distribution at steady state.
[i] One subject was excluded because of incomplete urine collection.

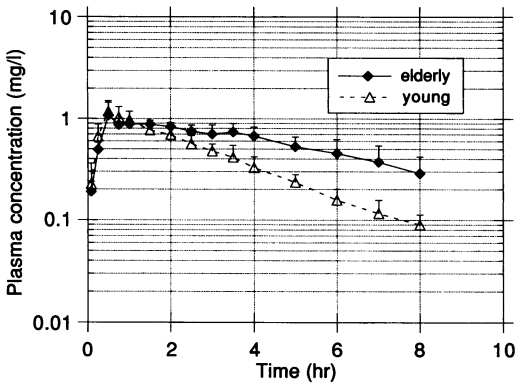

FIG. 2. Mean plasma concentrations (with SD) of ICI 213,689 in eight young and five elderly healthy men following a 30-min i.v. infusion of 0.5 g of meropenem.

Statistical analysis. The results were calculated as the group means with the standard deviation (SD) as an indicator 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 of <0.05. For P values between 0.01 and 0.05, the exact values have been given in the tables.

RESULTS

The single doses of meropenem were well tolerated by all volunteers, and no adverse events were noted. No significant changes developed during the routine laboratory safety screening.

The actual dose of meropenem in the elderly volunteers (500 ± 12.8 mg, corresponding to 7.3 ± 0.84 mg/kg of body weight) did not significantly differ from that in the younger control subjects (513 ± 15.3 mg, corresponding to 7.6 ± 0.84 mg/kg).

Distribution of meropenem was rapid in both elderly and young subjects. After reaching similar peak levels at the end of infusion in the two groups, plasma concentrations fell more rapidly over time in the younger subjects (Fig. 1). The pharmacokinetic variables of meropenem are summarized in Table 2. In this study, GFR correlated significantly with both total clearance (Spearman's rank correlation coefficient, 0.94; $P < 0.001$) and renal clearance (Spearman's rank correlation coefficient, 0.87; $P < 0.01$) of meropenem.

Because of improper handling of plasma samples, three elderly volunteers had to be excluded from the determination of the plasma profile of metabolite. The mean plasma concentration curve for ICI 213,689 in the remaining five elderly subjects and the corresponding curve for the younger control subjects are presented in Fig. 2. Table 3 summarizes the main kinetic variables for the metabolite. Since meropenem was detectable in plasma from many subjects throughout the study period, ICI 213,689 must have been continuously produced. Thus, the metabolite half-life ($t_{1/2}$) should be considered an estimate rather than a true terminal $t_{1/2}$. The total urinary recovery (meropenem and metabolite) over 8 h was not significantly altered in the elderly volunteers (84.7% ± 7.1%; $n = 7$) compared with that in the young volunteers (89.0% ± 8.0%; $n = 8$).

In the 12 subjects for whom renal clearance could be determined for both meropenem and its metabolite, there was no significant correlation between these variables (Spearman's rank correlation coefficient, 0.31).

DISCUSSION

This study demonstrates a significant reduction in renal excretory capacity for meropenem and its ring-opened metabolite in elderly subjects. This change is clearly age related and is explained by the well-established physiological decline in renal function with advancing age (1, 6). Such reduction in drug clearance in the elderly has been demonstrated earlier for a number of beta-lactam antibiotics eliminated by strict glomerular filtration, e.g., ceftazidime (14, 15), or by a combination of filtration and tubular secretion, e.g., cefuroxime (7). The renal excretion of non-beta-lactams is affected by age in a similar fashion (13, 17).

In the present study, the changes in total clearance of meropenem are slightly more consistent than the changes in renal clearance. This is thought to be due to the unavoidable difficulties in performing perfect urine collection and, thus, to the greater reliability of plasma profiles.

In addition to the decline in capacity for renal elimination, a reduction in nonrenal clearance was seen in the aged. In all probability, this is caused by a slower metabolic transformation of the meropenem molecule. Unfortunately, the concentration data for the metabolite in this study are not sufficient to confirm this presumed decline in the rate of metabolism. The age-related changes in the plasma profile of ICI 213,689 are dominated by the decrease in the renal excretion rate of the metabolite, which in its turn leads to increased $t_{1/2}$, MRT, and AUC. One way of demonstrating a reduction in metabolite production would be to compare the total urinary recoveries of the metabolite in the two groups of volunteers, which requires urine collection until there is no more metab-

TABLE 3. Pharmacokinetic variables[a] for ICI 213,689 in connection with i.v. infusion of 0.5 g of meropenem over 30 min

Group[b]	C_{max} (mg/liter)[c]	T_{max} (h)[d]	λ_z (h^{-1})[e]	$t_{1/2\lambda_z}$ (h)[e]	MRT (h)[e]	AUC (h · mg/liter)[e]	CL_R [ml/(min · 1.73 m^2)][f]	Urinary recovery over 8 h (%)[g]
Elderly	1.1 ± 0.34[h]	1.0 ± 0.50[h]	0.222 ± 0.075[h]	3.12[h]	5.70 ± 1.95[h]	6.54 ± 2.14[h]	346 ± 149[i]	17.5 ± 6.2[j]
Young	1.2 ± 0.34	0.57 ± 0.13	0.350 ± 0.032	1.98	3.14 ± 0.35	3.61 ± 0.62	608 ± 167	20.8 ± 6.6

[a] Group means ± SD.
[b] Statistical significance for comparisons between groups was determined by Wilcoxon's two-tailed rank sum test for unpaired observations.
[c] C_{max}, maximum concentration of drug in serum.
[d] T_{max}, time to maximum concentration of drug in serum.
[e] $P < 0.01$.
[f] $P = 0.042$.
[g] Corrected for differences in molar weight between meropenem and the metabolite.
[h] Three subjects were excluded because of improper handling of plasma samples.
[i] Four subjects were excluded because of improper handling of plasma samples (3 subjects) and incomplete urine collection (1 subject).
[j] One subject was excluded because of incomplete urine collection.

olite excretion. The urine sampling period in our study is too short to allow for such a comparison. Due to the long $t_{1/2}$ in the elderly, plasma sampling should also have continued for a period longer than 8 h to be ideal for the kinetic calculations regarding the metabolite.

The practical implication of the reduced clearance with the resulting prolonged $t_{1/2}$ of meropenem is that dose reduction of the compound should be considered in elderly subjects. In studies of patients with various degrees of renal dysfunction, it has been suggested that those with a GFR above 50 ml/min could receive the normal dosage (4). One must recognize, however, that a normal serum creatinine level in an elderly subject does not exclude the presence of significant renal dysfunction. Approximate creatinine clearance estimation by one of the existing formulas or nomograms based on serum creatinine level, age, sex, and weight (5, 18) is strongly recommended for all elderly patients in order to determine a proper dosage for all compounds with predominantly renal elimination.

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