Effects of Impaired Renal Function, Hemodialysis, and Peritoneal Dialysis on the Pharmacokinetics of Mezlocillin

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The pharmacokinetics of mezlocillin were examined in 8 patients with normal renal function (inulin clearance, >80 ml/min per 1.73 m²), 32 patients with moderately reduced renal function (inulin clearance, 80 to 5 ml/min per 1.73 m²), and 12 patients maintained by hemodialysis or peritoneal dialysis because of severely impaired renal function. A single dose of 60 mg of mezlocillin per kg of body weight was infused intravenously over 30 min. Antibiotic concentrations in plasma, urine, and dialysate were determined by the agar diffusion technique. The half-life of mezlocillin increased with decreasing renal function from an average of 53 min in subjects with normal function to 165 min in oligoanuric patients. The urinary recovery of this drug in 24 h decreased from 65% at a glomerular filtration rate of 92 ml/min to 7.6% at a glomerular filtration rate of 6.7 ml/min. Volume of distribution was not changed by the renal insufficiency, amounting on the average to 22.5% of body weight. Intermittent hemodialysis or peritoneal dialysis contributed to only a minor degree to the 24-h mezlocillin kinetics. The pharmacokinetic properties of mezlocillin permit a normal dosage over wide ranges of renal insufficiency; however, when the glomerular filtration rate is below 10 ml/min, the dosage interval should be increased from 8 to 12 h.

Mezlocillin, an acylureido penicillin with broad-spectrum antibacterial activity, is indicated for use in severe bacterial infections which are often complicated by temporary renal impairment. For this reason, the pharmacokinetic properties of this drug in patients with various degrees of renal insufficiency, from moderate to very severe (requiring dialysis), are of particular interest; results of studies of these properties are presented here.

MATERIALS AND METHODS

Subjects. The pharmacokinetics of mezlocillin were examined in a total of 52 patients (29 males and 23 females: 18 to 77 years old; mean 44 years old) referred to our department for treatment of arterial hypertension or kidney disease. All had apparently normal hepatic and cardiac function. In patients not requiring dialysis, the glomerular filtration rate (GFR) was determined by inulin clearance (Ci, anthrone method). The spectrum of normal to extremely reduced function was divided into six categories: group I, GFR of >80; II, GFR of 80 to 40; III, GFR of 40 to 20; IV, GFR of 20 to 10; V, GFR of 10 to 5; and VI, GFR of 5 to 0 ml/min per 1.73 m². With the exception of 12 patients in group VI, 8 patients were examined in each group. The influence of hemodialysis or peritoneal dialysis treatment on the pharmacokinetics of mezlocillin was studied in group VI. A total of 8 of these 12 patients (4 hemodialysis, 4 peritoneal dialysis) could be examined both under dialysis and in the dialysis-free interval. Informed consent was obtained from all patients.

Drug administration. Mezlocillin was infused intravenously as a single dose of 60 mg per kg of body weight over exactly 30 min by means of a constant-infusion pump (Injektomat, E. Fresenius KG). In patients without dialysis, blood samples were collected in heparinized syringes at 0.5, 1, 1.5, 2, 3, 4, 5, 6.5, and 8 h; in addition, in group VI blood samples were drawn at 9 and 12 h after termination of infusion. Plasma was separated immediately by centrifugation and stored at −18°C before processing. Urine was collected at 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h after mezlocillin administration. At the end of each collection period, a sample was stored at −18°C before processing.

Hemodialysis and peritoneal dialysis. Hemodialysis was started 1 h after termination of infusion and continued for 5 to 6 h, using the model Lundia Optima (Gambro Medizintechnitz GmbH & Co KG; 1-m² surface area, 13.5-μm cuprophan membrane) as the dialyzer. The blood flow in the extracorporeal circulation measured electromagnetically with a Statham flowmeter SP 2201 amounted to 200 ml/min with one exception (150 ml/min). The dialysate flow regularly amounted to 600 ml/min (single-pass system; Gambro AK 5). To determine total body clearance and dialyzer clearance, samples were taken at hourly intervals from blood entering and leaving the dialyzer. By simultaneous hematocrit determination, the plasma flow was calculated from the blood flow and used for computation of clearance.

Peritoneal dialysis via a Tenckhoff in-dwelling catheter was also started 1 h after termination of the infusion and continued for at least 8 h. The dialysate volume amounted to 2 liters in each case and was changed three times per hour. Blood samples were
obtained at hourly intervals after dialysis was begun. The dialysate was collected in 2-h portions, and samples from the middle of the collecting period were stored at -18°C.

Antibiotic assay. Mezlocillin concentrations were measured by the cup-plate agar diffusion method using antibiotic medium no. 3 and 2% agar (Difco Laboratories). The test strain used was Bacillus subtilis (Bacto subtilis spore suspension; Difco catalog no. 0981-52). The procedure was sensitive to less than 1 μg/ml. Standards for comparison were prepared in pooled human plasma, dialysate solution, or urine.

Pharmacokinetic analysis. At first, a semilogarithmic plot of the mezlocillin plasma concentrations versus time was generated and examined for each patient. Since in the time interval chosen for blood sampling no distribution phase was apparent, we assumed the data to be well described by a linear one-compartment open model. Curve fitting to an exponential function was done by the method of least squares, allowing calculation of the total elimination rate constant (kₐ) and the concentration at the end of infusion (cₗ). The correlation coefficients of the individual curves were all above 0.987 (mean, 0.995 ± 0.004). Thereafter, the apparent volume of distribution (Vₐ) was determined according to:

\[ Vₐ = \frac{\bar{v}}{kₐ - cₗ} (1 - e^{-kₐ t}) \]

where \( \bar{v} \) is the infusion speed (dose/time) and \( t \) is the duration of the previous infusion. The elimination half-life (\( t_{1/2} \)) and total body clearance (Cₐ) were calculated according to standard equations:

\[ t_{1/2} = \frac{\ln 2}{kₐ} \quad \text{and} \quad Cₐ = kₐ \cdot Vₐ \]

Under the assumption that no significant amount of drug was removed from erythrocytes, the dialyzer clearance (Cₐ) was determined from the plasma flow (Q), and the mean substance concentration in the blood entering (cᵢ) and leaving (cₒ) the dialyzer according to:

\[ Cₐ = \frac{(cᵢ - cₒ) \cdot Q}{cᵢ} \]

The mean plasma concentrations (\( \bar{c} \)) were calculated after fitting the concentration-time curves to an exponential function and determining \( cₐ \) (concentration at the start of dialysis) and \( kₐ \) according to:

\[ \bar{c} = \frac{cₐ}{kₐ \cdot \tau} (1 - e^{-kₐ \cdot \tau}) \]

where \( \tau \) is the duration of dialysis. The peritoneal clearance (Cₚ) was determined by the clearance formula:

\[ Cₚ = \frac{D \cdot V}{\bar{c} \cdot \tau} \]

where \( D \) is the mean dialysate concentration, \( V \) is the total dialysate volume, \( \bar{c} \) is the mean plasma concentration, and \( \tau \) is the duration of dialysis.

RESULTS

Examinations without dialysis. Table 1 shows the average time-dependent mezlocillin concentrations for the patients with normal and various degrees of impaired renal function. The results of the pharmacokinetic analysis are summarized in Table 2, which shows the data for four patients of group VI with oligoanuria separately. Figure 1 shows individual representative curves of mezlocillin concentrations versus time for various degrees of impaired renal function.

In subjects with normal renal function, the elimination rate constant was 0.791 h⁻¹, which progressively decreased to 0.271 h⁻¹ in patients with oligoanuria. Correspondingly, the elimination half-life showed a threefold increase, from 53.4 to 165 min. Figure 2 shows the linear regression for the total elimination rate constant (kₐ) on the GFR (Cₐ). The least-squares linear regression of \( kₐ \) on \( Cₐ \) is \( kₐ = 0.366 + 4.99 \cdot 10^{-3} Cₐ \). With the exception of group I, the distribution volume was constant and amounted on the average to 22.5% of body weight. There was no

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**Table 1. Mezlocillin plasma concentrations at various times after drug infusion in 48 patients (8 per group) with normal and impaired renal function**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mezlocillin concn (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5*</td>
</tr>
<tr>
<td>I</td>
<td>143.5</td>
</tr>
<tr>
<td></td>
<td>±4.6</td>
</tr>
<tr>
<td>II</td>
<td>185.8</td>
</tr>
<tr>
<td></td>
<td>±48.2</td>
</tr>
<tr>
<td>III</td>
<td>184.6</td>
</tr>
<tr>
<td></td>
<td>±41.7</td>
</tr>
<tr>
<td>IV</td>
<td>238.3</td>
</tr>
<tr>
<td></td>
<td>±76.5</td>
</tr>
<tr>
<td>V</td>
<td>209.1</td>
</tr>
<tr>
<td></td>
<td>±65.5</td>
</tr>
<tr>
<td>VI</td>
<td>182.0</td>
</tr>
<tr>
<td></td>
<td>±43.9</td>
</tr>
</tbody>
</table>

* Values indicate mean ± standard deviation.
* Time (hours) after the end of infusion.
dependence on the degree of renal insufficiency (Table 2).

In healthy subjects, recovery of mezlocillin in urine averaged 65% of the administered dose with 85% eliminated within the first 4 h (Fig. 3). Renal elimination of mezlocillin decreased with increasing renal insufficiency and amounted to 7.6% (±278 mg/24 h) at a GFR of 6.7 ml/min (Fig. 3). At the same GFR, 0.3% of the administered dose was recovered in the third collection period. Thus, with a single 4-g dose of mezlocillin, minimal urine levels of about 34 μg/ml were still achieved 8 to 12 h after the end of infusion.

Figure 4 shows the total body clearance (C\textsubscript{tot}), the urinary recovery rate within 24 h (R\textsubscript{e}), and the extrarenal clearance of mezlocillin (C\textsubscript{w}). Except for a slightly divergent behavior in the higher functional range, the C\textsubscript{tot} and the mezlocillin elimination rate showed an almost parallel decrease. The renal clearance (C\textsubscript{r}), which was determined from C\textsubscript{r} = C\textsubscript{tot}·R\textsubscript{e} (percentage of dose), and the C\textsubscript{w} were used to calculate the extrarenal clearance (C\textsubscript{w}) according to the equation C\textsubscript{w} = C\textsubscript{tot} - C\textsubscript{r}. With increasing renal insufficiency, the C\textsubscript{w} showed a tendency to decrease from 88 to 60 ml/min (~32%) (Fig. 4).

Hemodialysis. The six patients under 5- to 6-h hemodialysis showed marked differences in the mean values of k\textsubscript{e} (0.502 h\textsuperscript{-1}), t\textsubscript{1/2} (91.7 min), and C\textsubscript{tot} (102 ml/min) compared with the non-dialyzed patients (group VI in Table 2; Fig. 5). The dialyzer clearance amounted to 33 ml/min, and the substance removed amounted to 797 mg (±24% of the administered dose). The pharmacokinetic data of the four patients examined both with and without hemodialysis are presented as an intradividual comparison (Table 3). The dialysis-related increase in k\textsubscript{e} as well as in C\textsubscript{tot} amounted to 44%.

Peritoneal dialysis. In the six patients examined, the 8-h peritoneal dialysis led to comparatively small changes in mezlocillin kinetics. The mean values of k\textsubscript{e} (0.347 h\textsuperscript{-1}), t\textsubscript{1/2} (149 min), and C\textsubscript{tot} (79.2 ml/min) differed negligibly from those of the nondialyzed patients (group VI in Table 2; Fig. 5). The peritoneal clearance (C\textsubscript{PD}) amounted to 7 ml/min, and the substance removed amounted to 179 mg (±5% of the administered dose). The dialysate concentrations measured during peritoneal dialysis decreased from 7.3 μg/ml at the end of the 1st hour to 1.2 μg/ml at the end of the 7th hour. In Table 3, the results from four patients examined both with and without peritoneal dialysis are presented as an intradividual comparison.

Based on the pharmacokinetic analysis, Table 4 shows the calculated maximal, minimal, and mean serum concentrations for the steady state, and the area under the curve for various degrees of renal insufficiency (5 × 4 g of mezlocillin per 24 h).

**DISCUSSION**

The elimination half-life of mezlocillin in subjects with normal renal function is only slightly shorter than that of azlocillin (12), ampicillin (9), or carbenicillin (8). However, considerable differences result from increasing renal insufficiency. Whereas in oligoanuria the mezlocillin half-life rises to only 2.8 h, that of azlocillin increases to 5.0 h (16), that of carbenicillin increases to 12 to 16 h (5, 8), and that of ampicillin increases to 10 to 20 h (9, 11). Our results for various degrees of renal insufficiency confirm the findings of Bergan et al. (2), who found only...

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**Table 2. Pharmacokinetic parameters of mezlocillin in 48 patients (8 per group) with normal and impaired renal function**

<table>
<thead>
<tr>
<th>Group</th>
<th>GFR (ml/min)</th>
<th>Dose (mg)</th>
<th>c\textsubscript{t} (μg/ml)</th>
<th>k\textsubscript{e} (h\textsuperscript{-1})</th>
<th>t\textsubscript{1/2} (min)</th>
<th>V\textsubscript{d} (% body wt)</th>
<th>C\textsubscript{tot} (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>92</td>
<td>3,819</td>
<td>179</td>
<td>0.791</td>
<td>53.4</td>
<td>30.6</td>
<td>250</td>
</tr>
<tr>
<td>±13</td>
<td>±0.102</td>
<td>±62</td>
<td>±1.02</td>
<td>±6.8</td>
<td>±7.9</td>
<td>±77</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>64</td>
<td>4,084</td>
<td>245</td>
<td>0.717</td>
<td>56.1</td>
<td>22.5</td>
<td>181</td>
</tr>
<tr>
<td>±11</td>
<td>±0.105</td>
<td>±63</td>
<td>±13.4</td>
<td>±7.6</td>
<td>±7.0</td>
<td>±70</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>28</td>
<td>3,936</td>
<td>256</td>
<td>0.528</td>
<td>84.8</td>
<td>21.7</td>
<td>115</td>
</tr>
<tr>
<td>±6.2</td>
<td>±1.100</td>
<td>±60</td>
<td>±25.7</td>
<td>±7.5</td>
<td>±19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>14</td>
<td>3,988</td>
<td>329</td>
<td>0.477</td>
<td>94.7</td>
<td>17.6</td>
<td>91</td>
</tr>
<tr>
<td>±2.9</td>
<td>±0.123</td>
<td>±101</td>
<td>±34.7</td>
<td>±5.3</td>
<td>±35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>6.7</td>
<td>3,784</td>
<td>286</td>
<td>0.410</td>
<td>116.0</td>
<td>20.7</td>
<td>80</td>
</tr>
<tr>
<td>±1.3</td>
<td>±0.180</td>
<td>±80</td>
<td>±44.7</td>
<td>±7.2</td>
<td>±27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>1.5</td>
<td>3,801</td>
<td>254</td>
<td>0.300</td>
<td>155.5</td>
<td>22.5</td>
<td>71</td>
</tr>
<tr>
<td>±1.3</td>
<td>±0.119</td>
<td>±48</td>
<td>±53.2</td>
<td>±4.0</td>
<td>±34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligoanuria\textsuperscript{a}</td>
<td>0.4</td>
<td>3,788</td>
<td>260</td>
<td>0.271</td>
<td>165.3</td>
<td>21.8</td>
<td>60</td>
</tr>
<tr>
<td>±0.3</td>
<td>±0.073</td>
<td>±33</td>
<td>±58.4</td>
<td>±2.4</td>
<td>±15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Values indicate mean ± standard deviation.
\textsuperscript{b} Concentration after the end of infusion.
\textsuperscript{c} Four patients are included in group VI.
a moderate increase in half-life up to a GFR of 11 ml/min. In two of four patients with a GFR of 5 to 8 ml/min, Kosmidis et al. (10) observed a biphasic elimination phase with a steeper β-slope and flatter γ-slope. Such a course could not be observed in any of our 16 patients with a GFR below 10 ml/min. In three of four cases with oligoanuria, elimination of more than 97% of the administered drug could be observed in the chosen time interval. But even in these cases with the severest renal impairment, such a prolonged elimination phase could not be demonstrated (Fig. 1). Accordingly, the increase in half-life up to 14 h that was shown by Kosmidis et al. (10) differs from the results presented here. The longest half-life in our cohort amounted to 4.2 h in a patient with anuria (Fig. 1).

Disrupted sodium and water elimination with enlargement of the extracellular space as well as a decrease in protein binding are frequently observed in advanced renal insufficiency (4, 14). Both changes result in an increase in the volume of distribution. In the case of mezlocillin, no such dependence could be demonstrated. In its order of magnitude, the distribution volume largely corresponded to that of other penicillins (azlocillin [16], ampicillin [9], carbenicillin [13]).

The urinary recovery rate of mezlocillin is

\[ C_{IN} > 80 \text{ ml/min} \]

\[ C_{IN} 20-40 \text{ ml/min} \]

\[ C_{IN} 10-20 \text{ ml/min} \]

\[ C_{IN} < 1 \text{ ml/min} \]

**Fig. 1.** *Mezlocillin plasma concentrations as a function of time for 19 patients with different degrees of renal impairment.*
PHARMACOKINETICS OF MEZLOCILLIN

In spite of the lower mezlocillin elimination in urine and the considerable decrease with increasing renal insufficiency, therapeutic urine levels are obtained over wide ranges of functional loss.

$$k_e = 0.366 + 4.99 \times 10^{-3} C_{IN}$$

$$n = 48$$

$$r = 0.80$$

FIG. 2. Relationship between total elimination rate constant ($k_e$) of mezlocillin and renal function ($C_{IN}$). The straight line represents the best fit calculated by the method of least squares with a corresponding correlation coefficient of 0.800 ($P < 0.001$).

FIG. 3. Cumulative urinary recovery of mezlocillin ($R_u$ as percentage of dose administered) for various degrees of renal insufficiency ($GFR = C_{IN}$). Bars represent mean ± standard error, $n = 40$.

FIG. 4. Total body clearance ($C_{tot}$, ○), extrarenal clearance ($C_{nr}$, ◦), and urinary recovery/24 h ($R_u/24$ h, ◊) of mezlocillin in normal and impaired renal function ($C_{IN}$). Bars represent mean ± standard error of groups I to VI. Mean ± standard error of four patients with oligoanuria is depicted separately.

FIG. 5. Mezlocillin plasma concentrations in advanced renal insufficiency ($C_{IN} < 3$ ml/min) during 8 h of peritoneal dialysis and 8 to 6 h of hemodialysis. Bars represent mean ± standard error of six patients, and the curve is the best least-squares fit to the means.
The extrarenal clearance (C\text{e}) in anuria of 60 ml/min for mezlocillin is twice as high as that of azlocillin (30 ml/min [16]). This explains their different pharmacokinetics in cases of reduced renal function. But, in contrast to anuria in healthy subjects, a C\text{e} of 88 ml/min can be calculated for mezlocillin. In addition, Fig. 4 shows that the C\text{e} remains nearly constant up to a GFR of 30 ml/min but decreases continuously thereafter. According to Gundert-Remy et al. (7), the bile recovery in subjects with healthy liver and kidneys amounts to 14 to 26% of the administered mezlocillin dose. After this, the C\text{e} reaches values of 35 to 65 ml/min and, taking into consideration the incomplete bile drainage, corresponds to our findings in patients with oligoanuria. Therefore, the comparatively lower C\text{e} in oligoanuria seems not to result from reduced hepatic drug elimination capacity caused by uremia. On the other hand, in nonoliguric patients, C\text{e} was calculated according to C\text{e} = C\text{tot} - C\text{r}. Therefore, the renal elimination of about 10% of the administered mezlocillin dose in the form of microbiologically ineffective metabolites or a mezlocillin instability before urine processing could explain the discrepancy. Further studies are in progress to clarify this point. 

Mezlocillin can be dialyzed relatively well by hemodialysis (Fig. 5). The clearance of the dialyzer used corresponds to approximately half of the total body clearance of the patients requiring dialysis (Table 3). However, with intermittent hemodialysis treatment and taking into account the dialyzer clearance for the 24-h elimination, this is of no consequence. Even with daily dialysis (5 to 6 h), e.g., in cases of acute hypercatabolic renal failure, an increase of C\text{tot} from, for example, only 86 to 97 liters/24 h (±13%) must be expected. Compared with hemodialysis, peritoneal dialysis is completely ineffective (Fig. 5). Even with daily peritoneal dialysis over 8 h, only a 4% increase in C\text{tot} can be expected. Basically similar findings were reported for ampicillin (15) and carbenicillin (5). On the other hand, the low peritoneal clearance leads to minimal mezlocillin dialysate concentrations. Systemic therapy of diffuse peritonitis should take this into consideration.

The pharmacokinetic properties of mezlocillin, particularly the relatively high extrarenal
clearance, considerably simplify the use of this drug in cases of chronic renal insufficiency. The therapeutic range of the penicillins and the fact that the dosage of mezlocillin is only half that of carbenicillin permits a doubling of the mean serum concentration without significantly increasing the risk of toxicity. In this respect, as shown in Table 4, a change in dosage becomes necessary only when the GFR decreases to 10 to 15 ml/min; in this case, an increase in the dosage interval from 8 to 12 h is sufficient. The dosage adjustment is further simplified by the fact that any hemodialysis or peritoneal dialysis treatment, as specified above, need not be taken into consideration (Table 4).

Two restrictions must, however, be emphasized. First, these dosage guidelines presuppose a normal liver function. The occurrence of a liver lesion, such as, for example, in septicemia, necessitates a further dose reduction. Second, for mezlocillin, Bergan (1) has demonstrated dose-dependent pharmacokinetics in healthy subjects; i.e., $C_{\text{tot}}$ decreases as the dose increases. Since this problem has not been studied in renal insufficiency, the dosage recommendations must be restricted to the mezlocillin doses used in the present investigation (3 to 5 g). Further studies are needed in similar patients with renal insufficiency, using different dosage levels.

LITERATURE CITED