Pharmacokinetics of Azlocillin in Persons with Normal and Impaired Renal Functions

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The pharmacokinetics of azlocillin, a new wide-spectrum antibiotic of the N-substituted group of ureidomethyl penicillins, was investigated in 10 subjects with normal and in 32 subjects with impaired renal functions. After intravenous injection of 2 g of azlocillin, serum concentrations of drug were measured microbiologically. The half-lives of azlocillin were 47 ± 8.8 min in patients with normal renal function, and 293.3 min in patients with severely impaired renal function. The correlation of half-life to renal functions is shown by the equation: 

\[ t/2 = 425.03 - 0.643w \]

where \( Cl_{in} \) is inulin clearance. The volume of distribution of azlocillin was 17.7% of the body weight. Protein binding was similar in patients with normal renal function and in those with severely impaired renal functions. The urinary excretion rate of azlocillin in patients with normal renal function was 64.8 ± 8.8% in 24 h.


MATERIALS AND METHODS

Azlocillin was tested in 10 healthy volunteers with normal renal function and in 32 patients of a nephrological outpatient clinic, most of whom had impaired renal function. Ages ranged from 17 to 62 years, with the mean age being 42.4 ± 14.3 years. The mean height was 167.7 ± 10.3 cm, and the mean weight was 66.1 ± 13.1 kg.

Each subject received an intravenous bolus injection of 2 g of azlocillin dissolved in 20 ml of double-distilled water; the mean dose was 32 ± 6 mg/kg of body weight. The first blood sample was drawn after 0.5 h, and an additional nine samples were taken at 30-min intervals over the next 6 h (in severely impaired renal function the collecting period was prolonged up to 10 h). The glomerular filtration rate was determined by measurement of the 51Cr-ethylenediaminetetraacetic acid clearance (2) and converted into inulin clearance (Clu) rates.

Urine was collected at four intervals, 0 to 2, 2 to 4, 4 to 6, and 6 to 24 h after injection, from the subjects with normal renal function. The concentration of azlocillin was determined by the agar diffusion test, according to the method of Bauer et al. (1).

In nine patients (five with normal and four with severely impaired renal functions [glomerular filtration rate, <3 ml/min]), protein binding in the serum was also determined by means of an agar diffusion test (8).

The data were calculated by computer by means of the open two-compartment body model, according to Gibaldi and Perrier (3). It was assumed that the azlocillin was equally distributed by the time the first blood sample was taken 30 min after the injection, and consequently the α phase in the calculation was omitted, giving the equation

\[ C_t = C_0 \cdot e^{-k_1 \cdot t} \]  

where \( C_t \) is the concentration at time \( t \), \( C_0 \) is the initial concentration at \( t = 0 \), and \( k_1 \) is the elimination constant or regression coefficient (r). With equation 1, given the initial concentration, \( C_0 \) and the elimination constant, \( k_1 \), one can calculate the concentration of the drug at any desired time. The calculation of the half-life was done by a computer program based on the equation:

\[ t/2 = \frac{\ln 2}{k_2} \]  

where \( t \) is the time, \( k_2 \) is the elimination constant.

288
RESULTS

Serum concentrations of azlocillin, as measured at intervals in 10 healthy volunteers, are shown in a semilogarithmic plot in Fig. 1a. The concentrations after intravenous administration followed the equation

\[ \ln C = 5.31 - 0.017t \]  \hspace{1cm} (3)

For comparison, the decay of plasma levels was followed in eight patients with severely impaired renal function (glomerular filtration rate lower than 10 ml/min; Fig. 1b). Mathematically it can be described as

\[ \ln C = 4.79 - 0.0026t \]  \hspace{1cm} (4)

The individual data of the examined subjects in both groups are listed in Table 1. There is a remarkable difference in ages in the two groups. Whereas the half-lives in healthy volunteers have been in a narrow range, there are naturally major differences in patients with severely impaired renal functions. The average half-life for ten subjects with normal renal function and an average body weight of 71.5 kg was 47.6 ± 8.8 min, as compared with an average half-life of 293.3 min in the eight patients with severely impaired renal function.

The azlocillin serum half-lives for normal subjects and for subjects with all ranges of impaired renal function are plotted against \( \text{Cl}_{\text{in}} \) in Fig. 2. The relationship between half-life and renal function can be expressed mathematically by the following equation:

\[ t/2 = 425.03 \cdot \text{Cl}_{\text{in}}^{-0.4009} \]  \hspace{1cm} (5)

\( r = 0.91 \)

FIG. 1. Semilogarithmic plot against time in (a) ten volunteers with normal renal function and (b) eight patients with terminal renal failure to emphasize the difference in pharmacokinetics. The curve was calculated.

FIG. 2. Logarithmic plot of the half-lives (t/2) against glomerular filtration (GF) rates (Cl_{in}). The data points obtained are representative of all grades of renal impairment. The correlation of half-life to renal function is shown by equation 5, given in the text. In most cases the actual half-life does not differ much from the calculated value.
Table 1. Distribution of body weight, age, glomerular filtration (\(CL_{in}\)), apparent half-lives \((tW)\), and initial concentration \((C_0)\) after intravenous administration of 2 g of azlocillin* 

<table>
<thead>
<tr>
<th>Subject</th>
<th>weight (kg)</th>
<th>age (yr)</th>
<th>(CL_{in}) (ml/min)</th>
<th>(tW) (min)</th>
<th>(C_0) (ug/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ko</td>
<td>81.5</td>
<td>49</td>
<td>122</td>
<td>43.7</td>
<td>133.8</td>
</tr>
<tr>
<td>Ka</td>
<td>95</td>
<td>27</td>
<td>121</td>
<td>34.7</td>
<td>92.6</td>
</tr>
<tr>
<td>Schö</td>
<td>85</td>
<td>24</td>
<td>119</td>
<td>51.4</td>
<td>99.6</td>
</tr>
<tr>
<td>Bu</td>
<td>59</td>
<td>23</td>
<td>117</td>
<td>55.5</td>
<td>186.4</td>
</tr>
<tr>
<td>Dö</td>
<td>73.5</td>
<td>29</td>
<td>116</td>
<td>33.2</td>
<td>156.4</td>
</tr>
<tr>
<td>Kl</td>
<td>58.5</td>
<td>17</td>
<td>114</td>
<td>61.3</td>
<td>131.1</td>
</tr>
<tr>
<td>Ge</td>
<td>65</td>
<td>22</td>
<td>112</td>
<td>52.0</td>
<td>170.3</td>
</tr>
<tr>
<td>Schm</td>
<td>85</td>
<td>25</td>
<td>105</td>
<td>51.0</td>
<td>116.6</td>
</tr>
<tr>
<td>Fr.</td>
<td>48</td>
<td>21</td>
<td>104</td>
<td>45.5</td>
<td>200.1</td>
</tr>
<tr>
<td>Es</td>
<td>60</td>
<td>24</td>
<td>98</td>
<td>47.2</td>
<td>218.4</td>
</tr>
</tbody>
</table>

\[ \bar{X} = 71.05 \quad \bar{Y} = 26.1 \quad \bar{W} = 112.8 \quad \bar{t} = 47.6 \quad \bar{C}_0 = 150.5 \]
\[ S_X = 15.2 \quad S_Y = 8.7 \quad S_W = 8.0 \quad S_t = 8.75 \quad S_{C_0} = 42.9 \]
\[ \text{Var.Coeff.} = 21.4 \quad \text{Var.Coeff.} = 33.3 \quad \text{Var.Coeff.} = 7.1 \quad \text{Var.Coeff.} = 18.4 \quad \text{Var.Coeff.} = 28.5 \]

**Normals**

<table>
<thead>
<tr>
<th>Subject</th>
<th>weight (kg)</th>
<th>age (yr)</th>
<th>(CL_{in}) (ml/min)</th>
<th>(tW) (min)</th>
<th>(C_0) (ug/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sch</td>
<td>53</td>
<td>50</td>
<td>9.0</td>
<td>417.7</td>
<td>106.9</td>
</tr>
<tr>
<td>Schw</td>
<td>61.5</td>
<td>60</td>
<td>8.4</td>
<td>110.5</td>
<td>126.6</td>
</tr>
<tr>
<td>He</td>
<td>44</td>
<td>31</td>
<td>5.0</td>
<td>198.5</td>
<td>126.5</td>
</tr>
<tr>
<td>Lu</td>
<td>57.8</td>
<td>37</td>
<td>3.4</td>
<td>219.9</td>
<td>141.4</td>
</tr>
<tr>
<td>Str.</td>
<td>64.3</td>
<td>57</td>
<td>1.9</td>
<td>495.9</td>
<td>89.1</td>
</tr>
<tr>
<td>GÖ</td>
<td>57.5</td>
<td>76</td>
<td>1.8</td>
<td>246.2</td>
<td>108.0</td>
</tr>
<tr>
<td>Po</td>
<td>61.3</td>
<td>44</td>
<td>1.5</td>
<td>199.6</td>
<td>109.5</td>
</tr>
<tr>
<td>Scho</td>
<td>52.8</td>
<td>60</td>
<td>1.5</td>
<td>378.0</td>
<td>169.0</td>
</tr>
</tbody>
</table>

\[ \bar{X} = 57.8 \quad S_X = 7.6 \quad \text{Var.Coeff.} = 13.1 \]

**Uremics**

\[ \bar{X} = 57.8 \quad \bar{Y} = 51.9 \quad \bar{W} = 4.1 \quad \bar{t} = 293.3 \quad \bar{C}_0 = 122.1 \]
\[ S_X = 7.6 \quad S_Y = 3.1 \quad \text{Var.Coeff.} = 24.8 \]

In most cases the measured plasma data were in a good agreement with the calculated values. The volume of distribution \((V)\) of azlocillin was calculated by the formula

\[ V = \frac{D}{C_0} \tag{6} \]

where \(D\) is the applied dose and \(C_0\) is the initial concentration. The volume of distribution was 12.6 liters, or 17.7% of the body weight.

The urinary excretion of azlocillin was followed in 12 subjects with normal renal function. The urinary excretion of azlocillin in the first 2
Fig. 3. Urinary excretion of azlocillin in 12 subjects with normal renal function; the mean was 64.8 ± 8.8% in 24 h.

h was 51.9%, or 80.1% of the total. In the next 2 h, only 9.4% azlocillin was found in the urine samples, and in the subsequent two 2-h urine samples, only 2.2 and 1.3%, respectively, were found (Fig. 3). The average urinary excretion of azlocillin was 64.8 ± 8.8% in 24 h. There was no relationship between amount excreted and urine volume.

The average protein binding for five persons with normal renal function was 27.9 ± 6.1% (average total protein, 7.48 g/100 ml), and that for four patients on regular hemodialysis was 25 ± 1.6% (average total protein, 6.88 g/100 ml).

DISCUSSION

In a previous study, Wirth et al. (10) found serum concentrations of azlocillin nearly identical to those found in this investigation in 10 subjects with normal renal function given 2-g intravenous injections of the antibiotic. In their study the average half-life was 51.5 min, which does not differ significantly from our rates for subjects with normal renal function. Wirth et al. calculated an average volume of distribution of 13.7 liters, or 17.7% of the body weight; our value of 12.6 liters, or 17.7% of the body weight, is comparable.

Azlocillin is a new derivative of penicillin. Therefore, a comparison of pharmacokinetic characteristics with semisynthetic penicillins would be worthwhile. The half-life of azlocillin lies in the same range as that of ampicillin, which is 43.7 min (4).

According to Hoffmann et al. (5) the mean serum half-life after intravenous administration of 2 g of carbenicillin is 60 ± 0.15 min, which is slightly longer than that of azlocillin. A correlation of half-life to renal function, which can be expressed mathematically by an exponential function, is also found for other antibiotics in the penicillin group, such as carbenicillin, ticarcillin, and ampicillin (4).

We found a urinary excretion rate of 64.8% in 24 h after a dose of 2 g of azlocillin; in earlier studies rates of 44 and 57% (studies done at Bayer AG) and 59% (10) were found. The urinary excretion rates found for ampicillin are 80% (9) and 63.8 to 69.1% (7), and for carbenicillin they are 84% (9) and 76% (6). Thus, the total percentage of the dose of azlocillin excreted in urine is slightly lower than that of carbenicillin but similar to that of ampicillin.

The slight difference in protein binding between normal persons and uremic subjects is not significant.

LITERATURE CITED