Amoxycillin: pharmacokinetic studies in normal subjects, patients with pernicious anaemia and those with renal failure

D. H. Lawson*  
M.D., M.R.C.P.

A. K. Henderson*  
M.B., M.R.C.P.

R. R. McGechy  
A.I.M.L.T.

Department of Medicine and Bacteriology, Western Infirmary, Glasgow

Summary
This paper presents data on the absorption and disappearance of a new semisynthetic antibiotic—amoxycillin—in patients with pernicious anaemia and those with renal failure. Absorption of this drug is unimpaired in these patients. Adequate serum and urine levels are obtained even in patients with creatinine clearance levels below 10 ml/min. The half-life of this drug is markedly prolonged in patients undergoing regular dialysis therapy, and a single 250 mg dose will provide adequate serum levels for 24 hr, if this is given after dialysis is complete.

Introduction
Amoxycillin is a recently introduced semi-synthetic penicillin. It is reported to be freely absorbed orally, to be uninfluenced by the presence of food in the stomach, to reach higher serum concentrations than ampicillin on a dose-for-dose comparison and to attain therapeutic concentrations in the urine (Sutherland, Croydon and Rolinson, 1972). In addition, this drug has the same wide spectrum of antibacterial activity as ampicillin (Sutherland and Rolinson, 1970).

The present investigation was undertaken to study the handling of this antibiotic in normal subjects, patients with pernicious anaemia and in those with varying degrees of renal impairment.

Methods
Amoxycillin was given in a dose of 250 mg 8-hourly for 7 days. Patients received breakfast as usual on the day of the study and then were given their first dose of amoxycillin at 9 a.m. Serial blood and urine collections were taken for 6–8 hr thereafter. Once the initial investigations were complete the patients continued to take the amoxycillin regularly until the final dose at 9 a.m. on day 8. Serial blood and urine collections were again taken during the 8 hr following the last dose of antibiotic.

All blood samples were promptly separated and the serum frozen until the assays could be performed—usually within 4 days of collection. The antibacterial activity of each specimen was measured in quadruplicate using the method described by Bennett et al. (1966). The test organism used was Sarcina lutea NCTC 8340. Similar techniques were used to verify the antibiotic concentration found in a representative group of 250 mg capsules.

Initial studies were performed on four normal patients and the resulting data compared with those found when three patients with treated pernicious anaemia were investigated. The studies were then repeated on nine patients suffering from various degrees of renal impairment. In all cases patients gave their informed consent to the investigation. No patient was included in the study if he had received antibacterial therapy in the preceding 6 weeks.

In addition, three patients with chronic renal failure who required regular dialysis therapy were given single doses of 250 mg amoxycillin immediately after commencing dialysis. In each case, dialysis involved an Ultra-flow twin-coil artificial kidney. The resulting blood levels were then compared with those obtained when the patients received a similar dose of amoxycillin after dialysis was completed.

In all cases blood levels were related to time on a semi-logarithmic scale and regression lines were fitted to the blood levels recorded between 2 and 8 hr after ingestion of the capsule. The resulting equation of the regression line was then used to calculate the half-life of the drug in the serum \(t_{1/2}\text{-min}\), the hypothetical concentration of drug at time zero \(C_{0.0}\), \(\mu g/ml\) and from this the apparent volume of distri-
Amoxycillin in renal failure

Table 1. Amoxycillin levels attained in patients with normal renal function: a comparison of results obtained after a single dose and after a week's course

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Peak serum level (μg/ml)</th>
<th>Volume of distribution (l)</th>
<th>t½ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Normal</td>
<td>5.0</td>
<td>11.3</td>
<td>52.9</td>
</tr>
<tr>
<td>B</td>
<td>Normal</td>
<td>7.2</td>
<td>16.2</td>
<td>109.3</td>
</tr>
<tr>
<td>C</td>
<td>Normal</td>
<td>5.6</td>
<td>25.9</td>
<td>82.5</td>
</tr>
<tr>
<td>D</td>
<td>Normal</td>
<td>5.2</td>
<td>15.9</td>
<td>76.1</td>
</tr>
<tr>
<td>E</td>
<td>PA</td>
<td>7.2</td>
<td>13.7</td>
<td>93.1</td>
</tr>
<tr>
<td>F</td>
<td>PA</td>
<td>4.8</td>
<td>13.8</td>
<td>66.0</td>
</tr>
<tr>
<td>G</td>
<td>PA</td>
<td>7.2</td>
<td>9.3</td>
<td>62.4</td>
</tr>
</tbody>
</table>

Table 2. Amoxycillin levels attained in patients with renal impairment: a comparison of results obtained after a single dose and after a week's course

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ccreat</th>
<th>Peak serum level (μg/ml)</th>
<th>Volume of distribution (l)</th>
<th>t½ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>42</td>
<td>8.0</td>
<td>16.1</td>
<td>128.3</td>
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<tr>
<td>J</td>
<td>33</td>
<td>7.2</td>
<td>21.7</td>
<td>203.8</td>
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<tr>
<td>K</td>
<td>27</td>
<td>17.6</td>
<td>5.3</td>
<td>169.0</td>
</tr>
<tr>
<td>L</td>
<td>19</td>
<td>8.0</td>
<td>10.6</td>
<td>157.0</td>
</tr>
<tr>
<td>M</td>
<td>13</td>
<td>6.4</td>
<td>32.7</td>
<td>433.0</td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>14.4</td>
<td>23.6</td>
<td>911.0</td>
</tr>
<tr>
<td>P</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Q</td>
<td>3</td>
<td>9.2</td>
<td>23.3</td>
<td>648.0</td>
</tr>
</tbody>
</table>

Results

In normal subjects peak serum levels were attained at 2 hr after ingestion of the capsule, and ranged from 5 to 7.2 μg/ml. Similar values were obtained in patients with treated pernicious anaemia. There were no significant differences between the peak serum levels observed after a single capsule of amoxycillin and those seen after a 7-day course. Serum levels fell below 1 μg/ml within 6 hr of administering the drug in all patients.

In patients with renal impairment, peak serum levels occurred later than in the controls—between 3 and 4 hr after capsule administration. The mean peak serum level attained on day 1 was 10.1 (s.e. 1.6) μg/ml and on day 8 was 12.1 (s.e. 1.7) μg/ml.

In patients with normal renal function, the half-life of amoxycillin in the serum after a single dose was 77.5 (s.e. 7.3) min, and after the end of a 7-day course it was 92.2 (s.e. 9.7) min (–tpaired = 4.8; P < 0.01), Table 1. The half-life was prolonged in all subjects with creatinine clearance levels below 50 ml/min, Table 2, Fig. 1. In addition the half-life calculated on day 8 was significantly longer than that on day 1 in all patients with creatinine clearance levels exceeding 15 ml/min [t½ (day 1) = 109 (s.e. 15) min; t½ (day 8) = 137 (s.e. 22) min – tpaired = 2.90 P < 0.05]. No such relationship was noted in patients with lower glomerular filtration rates.

The calculated volume of distribution of amoxycillin was 17.2 (s.e. 1.3) l. There were no statistically significant differences in this volume of distribution between patients with normal and abnormal renal function or between values estimated at the beginning or end of the study.

The relationship between creatinine clearance and the observed half-life of amoxycillin was an exponential one—the equation most closely expressing the observed results following the initial study was:

\[ t_\frac{1}{2} = 456. e^{-0.018c} \quad (r = 0.768; \ P < 0.01). \]

Following the 7-day course of therapy the comparable equation was:

\[ t_\frac{1}{2} = 391. e^{-0.015c} \quad (r = 0.779; \ P < 0.01) \] (Fig. 1).
ulceration during a course of ampicillin and on this occasion developed severe ulceration on day 3 of amoxycillin therapy. Subsequently, blood levels were found to be grossly elevated, the peak serum level being 31.2 μg/ml at 2 hr. More surprisingly, the observed half-life was low (80 min) and the maximum concentration of amoxycillin in the urine at 2-4 hr was relatively high (220 μg/ml). Some 158 mg of amoxycillin was recovered in the urine during the first 6 hr after a 250 mg dose.

Three patients with severe renal failure requiring regular dialysis therapy were studied during and after haemodialysis. Blood levels attained after a single 250 mg capsule of amoxycillin were higher when the drug was given after dialysis than when it was given at the beginning of the procedure. However, in both situations therapeutic levels were recorded for periods exceeding 6 hr after capsule ingestion.

Finally, the antibacterial activity of 10 capsules of amoxycillin were assayed—all were found to lie between 260 and 280 mg.

**Discussion**

The results of this investigation confirm that amoxycillin is satisfactorily absorbed orally even in the presence of food in the stomach (Sutherland et al., 1972). Absorption is satisfactory in patients with achlorhydria and remains so even in the presence of severe renal impairment.

Serum levels exceeding 1 μg/ml were present for up to 6 hr after an oral dose of 250 mg in all subjects. Such levels are known to be bactericidal for most strains of *Haemophilus influenzae* and all penicillin-sensitive strains of staphylococci, streptococci and pneumococci (Sutherland et al., 1972). Urine concentrations exceeding 30 μg/ml were present for 6 hr after a 250 mg capsule in all subjects tested, and the mean concentration observed in normal subjects between 2 and 4 hr after treatment was over 500 μg/ml. The mean proportion of the administered dose which was recovered in the urine during the 6 hr after administration was 64% in those with normal renal function and 38% in those with renal impairment. These results indicate that amoxycillin is a suitable drug to use in patients with renal failure who are suffering from a penicillin-sensitive infection. In the case of a urinary tract infection, both serum and urinary concentrations of amoxycillin are well within the therapeutic range even in patients with creatinine clearance levels below 10 ml/min.

The calculated volume of distribution of amoxycillin was relatively constant over a wide range of renal function, and was slightly greater than the expected extracellular fluid volume of these subjects. This finding is compatible with the known protein-binding characteristics of amoxycillin and explains...
the apparent increase in the half-life after a 7-day course of treatment.

Amoxycillin levels attained in patients requiring regular dialysis therapy are higher if the drug is given after the end of dialysis. The half-life is markedly prolonged in such patients and a single daily dose of 250 mg should be sufficient to maintain therapeutic concentrations for 24 hr.

Finally, in one subject with severe renal failure, the handling of amoxycillin was unusual, in that much higher than normal concentrations were detected in the patient’s serum and the calculated half-life was unusually short for someone with marked renal failure. Such behaviour on the part of a patient with renal failure has previously been reported in the case of cephalaxin (Kunin and Finkleberg, 1970), but as yet no satisfactory explanation has been given.

Acknowledgments
We wish to thank Dr J. Price of Beechams for providing the amoxycillin used in this study, Dr J. D. Sleigh for his help and advice and Dr J. D. Briggs for permitting free access to patients under his care.

References
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