Penetration of Teicoplanin into Heart Valves and Subcutaneous and Muscle Tissues of Patients Undergoing Open-Heart Surgery

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Penetration of teicoplanin into serum, heart valves, and subcutaneous and muscle tissues was determined in 22 patients undergoing open-heart surgery. Each patient received 12 mg of teicoplanin per kg of body weight as a 30-min intravenous infusion preoperatively. Within 10 h, serum concentrations of teicoplanin declined from 43.1 to 2.5 μg/ml. Teicoplanin concentrations in subcutaneous tissues reached their peak of 9.2 μg/g after 2 to 3 h and decreased slowly to 2.3 μg/g after 9 to 10 h. Concentrations in muscle decreased from 8.7 μg/g to nondetectable levels. Teicoplanin concentrations in cardiac valvular tissue reached their peak of 6.1 μg/g and decreased thereafter to 1.7 μg/g. Teicoplanin concentrations in heart valves were high enough to inhibit methicillin-resistant Staphylococcus aureus and coagulase-negative staphylococci, which are known to cause postoperative wound infections and infective endocarditis.
tissues are shown in Table 1; mean concentration profiles for serum and heart valves are displayed in Fig. 1. Within 10 h, teicoplanin concentrations in serum declined from 43.1 to 3.4 mg/ml. Peak concentrations in serum were reached within 1 h after administration of the drug; peak concentrations in subcutaneous and muscle tissues were reached after 1 to 2 h and declined from 8.8 to 2.3 mg/g and from 6.7 to 0 mg/g, respectively. In heart valves, however, teicoplanin concentrations peaked 3 to 4 h after administration of the drug and declined from 6.1 to 1.7 mg/g.

Teicoplanin concentrations in serum after single and multiple intravenous doses of 3 and 6 mg/kg/day have been previously investigated in numerous studies (10). Clinical observations, however, suggest that these dosages might be too low for treating serious staphylococcal infections, such as endocarditis due to Staphylococcus aureus. For this reason, pharmacokinetic studies with higher dosages (up to 30 mg/kg/day) have been performed more recently (4, 13).

Teicoplanin concentrations in the sera of patients given a 30-min, constant-rate, intravenous infusion of 12 mg of teicoplanin/kg prior to cardiac surgery showed a triexponential kinetic profile comparable to that found in healthy volunteers (4, 13). Serum concentrations found in cardiac surgery patients were lower than those in healthy human volunteers. This, however, might be due to the existence of a higher blood volume during extracorporal circulation and to the fact that samples were obtained later from cardiac surgery patients than from healthy volunteers, whose samples were taken immediately after the end of the infusion (4).

Tissue concentrations of teicoplanin in subcutaneous tissues, heart valves, and muscle tissues were almost identical. S. aureus, for which the MIC of teicoplanin is below 2 μg/ml, with no significant differences between methicillin-susceptible and methicillin-resistant strains (8), would have been inhibited for approximately 4 to 5 h in heart valves, 5 to 6 h in muscle tissues, and 8 to 10 h in subcutaneous fat and serum. Among coagulase-negative staphylococci, however, species-dependent differences in susceptibility to teicoplanin have been observed (7). Since the mean teicoplanin MIC at which 90% of the isolates are inhibited (MIC90) is 2 to 4 μg/ml, most strains would be inhibited for at least 4 h in heart valves, muscle tissue, and subcutaneous fat. Teicoplanin is more active than vancomycin against streptococci, including enterococci, with MIC90s ranging from 0.2 to 3 μg/ml, which represent drug levels main-

<table>
<thead>
<tr>
<th>Time after administration (h)</th>
<th>Serum</th>
<th>Heart valve</th>
<th>Muscle tissue</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>43.1 ± 24.9 (13)</td>
<td>1.5 ± 1.3 (4)</td>
<td>4.1 ± 3.6 (7)</td>
<td>7.2 ± 4.9 (7)</td>
</tr>
<tr>
<td>1–2</td>
<td>27.5 ± 20.3 (12)</td>
<td>2.8 ± 1.4 (3)</td>
<td>6.7 ± 8.8 (9)</td>
<td>8.8 ± 6.7 (7)</td>
</tr>
<tr>
<td>2–3</td>
<td>16.2 ± 10.5 (16)</td>
<td>5.5 ± 5.1 (8)</td>
<td>6.6 ± 4.5 (7)</td>
<td>5.8 ± 4.9 (7)</td>
</tr>
<tr>
<td>3–4</td>
<td>13.7 ± 10.4 (6)</td>
<td>6.1 ± 8.1 (3)</td>
<td>4.1 ± 1.9 (4)</td>
<td>5.6 ± 4.5 (4)</td>
</tr>
<tr>
<td>4–5</td>
<td>9.4 ± 5.1 (9)</td>
<td>2.7 ± 1.9 (4)</td>
<td>3.9 ± 1.8 (4)</td>
<td>4.8 ± 2.5 (4)</td>
</tr>
<tr>
<td>5–6</td>
<td>6.9 ± 3.2 (3)</td>
<td>□ a</td>
<td>3.4 ± 1.4 (3)</td>
<td>3.9 ± 1.3 (2)</td>
</tr>
<tr>
<td>6–8</td>
<td>5.7 ± 2.1 (5)</td>
<td>□ a</td>
<td>2.1 ± 1.2 (4)</td>
<td>2.7 ± 0.4 (5)</td>
</tr>
<tr>
<td>8–10</td>
<td>3.4 ± 0.6 (2)</td>
<td>1.7 (1)</td>
<td>0 (1)</td>
<td>2.3 (1)</td>
</tr>
</tbody>
</table>

a Data are means ± standard errors of the means. Concentrations in serum are in micrograms per milliliter; concentrations in tissues are in micrograms per gram. The numbers of specimens are shown in parentheses.

b □, no specimens assayed.

FIG. 1. Concentrations of teicoplanin in cardiac surgery patients after a single, 30-min, constant-rate, intravenous infusion of 12 mg of the drug per kg of body weight.
tained for 4 to 5 h in cardiac surgery patients. While the results in vitro do not necessarily reflect the situation in vivo, the data should be interpreted cautiously. Treatment of endocarditis caused by *S. aureus* with teicoplanin has been difficult, especially when used as monotherapy (2). Since approximately 90% of teicoplanin is bound to human serum proteins, and protein binding may affect both the killing activity and the distribution of the drug, high dosages of teicoplanin may be required to ensure efficacy (1).

We conclude that teicoplanin (at 12 mg/kg) may be a useful drug for prophylaxis of infections in patients who are allergic to penicillins or cephalosporins and are undergoing open-heart surgery. The administration of a second, lower dose of teicoplanin (6 mg/kg) at the end of cardiac surgery, i.e., 4 to 5 h after administration of the first dose, may be useful in preventing postoperative infections in patients undergoing open-heart surgery.

REFERENCES