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

UWE K. FRANK, 1* E. SCHMIDT-EISENLOHR, 1 D. MLANGENI, 2 M. SCHINDLER, 2 A. HOH, 3 F. BEYERSDORF, 3 AND F. D. DASCHNER 1

Institute for Environmental Medicine and Hospital Epidemiology, 1 Department of Anesthesiology, 2 and Department of Cardiac Surgery, 3 University Hospital Freiburg, Freiburg, Germany

Received 10 January 1997/Returned for modification 10 May 1997/Accepted 31 August 1997

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.

In an attempt to prevent both wound infections and prosthetic valve endocarditis, cardiac surgeons presently administer antibiotics to virtually all patients undergoing cardiac surgery. Current recommendations call for parenteral administration of antistaphylococcal drugs just prior to the operation and subsequent administration of one or two further doses. Because the therapeutic efficacy of glycopeptide antibiotics in the treatment of various infections attributable to gram-positive organisms is well established (12), teicoplanin, a compound structurally related to vancomycin, may be chosen for antibiotic prophylaxis in patients undergoing open-heart surgery and for treatment of infective endocarditis. Despite the widespread clinical use of teicoplanin among endocarditis patients who are allergic to penicillins, there are only limited published data on the concentrations of this drug achieved in human heart tissues following parenteral administration (9). This study was designed to investigate the penetration of teicoplanin into serum, heart valves, and subcutaneous and muscle tissues of patients undergoing open-heart surgery.

A single, 30-min, constant-rate, intravenous infusion of 12 mg of teicoplanin/kg of body weight was given to each of 22 patients with valvular heart disease (8 women and 14 men; mean ages, 65.8 and 60.1 years, respectively; mean body weights, 61.8 and 76.3 kg, respectively). The study was conducted at the Department of Cardiac Surgery, University Hospital Freiburg, Freiburg, Germany, and approved by the local Committee on Human Research. Informed consent was obtained from all patients. Each patient provided his or her complete history and underwent a physical examination. Laboratory tests performed prior to surgery included a complete blood count, urinalysis, and determination of blood urea nitrogen, transaminases, bilirubin, and creatinine. These values were normal in all patients. Teicoplanin was administered between 10 h and immediately before open-heart surgery. No other antibiotics were given. All of the operations were performed by the same surgical team.

Nonpulsatile blood flow was maintained at 50 ml/kg of body weight/min during cardiac bypass; blood temperatures reached 25 to 35°C (77 to 95°F). Mean arterial pressure varied between 60 and 80 mm Hg (7,998 to 10,664 Pa). The pump was primed with 1,000 ml of Ringer’s lactate solution, 500 ml of whole blood, and 200 ml of Osmofundin (Braun, Melsungen, Germany) plus 40 ml of Tris buffer. The mean extracorporal circulation time was 80 min.

One or two samples of venous blood, subcutaneous fat, and muscle tissue were taken simultaneously at various intervals after injection of the drug. Valvular tissue and blood samples were collected during valve replacement. Sterile gauze was used for removal of adherent blood from the tissue specimens, which were then frozen at −72°C (−98°F) and assayed during the next 4 to 6 weeks by an agar diffusion method with antibiotic medium no. 1 (Oxoid Ltd., Basingstoke, England), using Bacillus subtilis ATCC 6633 as the test organism. This method for antibiotic assays is well established (3, 5, 6). It allows the testing of large numbers of clinical specimens in a short period of time and provides a 95% certainty that a reported concentration is within a range of ±10% of the true concentration of the sample (2).

Tissue was mixed with phosphate buffer (pH 7.4) in a 1:3 (wt/vol) ratio and homogenized with a Coleworth Stomacher no. 80 (Seward and Co. Ltd., London, England) (11). Standards for the plasma antibiotic assay were prepared in phosphate-buffered human serum (1:1 [vol/vol]); standards for the tissue antibiotic assay were prepared in phosphate buffer (pH 7.4). There was a linear relationship between the mean zone diameter of inhibition and the logarithm of the antibiotic concentration of each standard. All determinations were made three times by the same technician. Histological examinations of all excised heart valves showed scars, remnants of old inflammations, and hyaline deposits but no vascularization of the tissue. No corrections for the serum content of any tissue specimens were made.

Mean concentrations for teicoplanin in serum and various...
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 μg/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 μg/g and from 6.7 to 0 μg/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 μg/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 the drug/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 (MIC<sub>90</sub>) 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 MIC<sub>90</sub>s 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>—</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>—</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>

<sup>a</sup> 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.

<sup>b</sup> —, 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