Clinical Evaluation of Teicoplanin for Therapy of Severe Infections Caused by Gram-Positive Bacteria

Y. GLUPCZYNKI,1* H. LAGAST,2 P. VAN DER AUWERA, J. P. THYS,3 F. CROKAERT,1 E. YOURASSOWSKY,1 F. MEUNIER-CARPENTIER,3 J. KLASTERSKY,3 J. P. KAINS,1 E. SERRUYS-SCHOUTENS,3 AND J. C. LEGRAND4

Service de Biologie Clinique, Hôpital Universitaire Brugmann, 1020 Brussels; Service de Médecine et Laboratoire d'Investigation Clinique H. Tagnon, Institut Jules Bordet, 1000 Brussels; Unité de Maladies Infectieuses et Service de Microbiologie, Hôpital Erasme, 1070 Brussels; and Service de Médecine, Hôpital Civil de Charleroi, 6000 Charleroi, Belgium

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Teicoplanin was evaluated in 47 patients with severe infections, including 14 patients with bone infections, 11 patients with soft-tissue infections, 7 patients with endocarditis, 5 patients with pneumonia, 3 patients with septic thrombophlebitis, 3 patients with septicemia of unknown origin, and 4 patients with miscellaneous infections. Overall, bacteremia was documented in 24 patients. The pathogens isolated were 35 strains of Staphylococcus aureus (including 8 methicillin-resistant strains), 4 strains of Staphylococcus epidermidis, 4 strains of Streptococcus faecalis, 2 strains of Streptococcus pneumoniae, 5 strains of other streptococci, and 1 Micrococcus luteus strain. A total of 22 patients (46.8%) were clinically cured, 8 patients (17.0%) improved, 2 patients (4.3%) had relapses after initial improvement, and 15 patients (31.9%) failed to respond. The results were better in nonbacteremic patients (19 of 23 patients [82.6%] were cured or improved) than in patients with bacteremia (12 of 24 patients [50%] were cured or improved). Bacteriological cure occurred in 25 patients (53.2%), and superinfections were documented in 6 patients (12.8%). No major adverse effects were observed. We conclude that teicoplanin is a potentially effective and well-tolerated antimicrobial agent for therapy of nonbacteremic infections caused by gram-positive bacteria.

Teicoplanin (formerly known as teichomycin A2) is a new glycopeptide antibiotic that is produced by Actinoplanes teichomyceticus (1, 15) and has a narrow spectrum which is restricted to most gram-positive microorganisms (3, 7, 8, 10, 11, 14, 18, 19). The activity of teicoplanin against staphylococci is similar to that of vancomycin, but teicoplanin is distinctly more active than vancomycin against streptococci and, particularly, against enterococci (3, 7, 8, 10, 18). Unlike vancomycin, teicoplanin can be administered intramuscularly. Moreover, the very long half-life of teicoplanin, in excess of 40 h (19), permits administration only once daily.

The present study was designed to determine the efficacy and safety of teicoplanin in the treatment of hospitalized patients with severe infections due to gram-positive bacteria. (The results were presented in part at the 24th Interscience Conference on Antimicrobial Agents and Chemotherapy [Y. Glupczynski, H. Lagast, J. C. Legrand, C. Potvliege, J. P. Thys, and P. Van der Auwera, Program Abstr. 24th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 583, 1984].)

MATERIALS AND METHODS

A total of 47 patients hospitalized at the Brugmann Hospital (Brussels, Belgium), at the Erasme Hospital (Brussels, Belgium), at the Institut Jules Bordet (Brussels, Belgium), and at the Hôpital Civil de Charleroi (Charleroi, Belgium) from September 1983 through September 1984 were included in the study after informed consent was obtained from patients or next of kin before therapy was started. The admission criteria included fever, other signs and symptoms of bacterial infection (endocarditis, pneumonia, cellulitis, osteomyelitis, thrombophlebitis, septicemia, and urinary tract infection), and isolation within 48 h before initiation of teicoplanin therapy of a pathogen susceptible to this antibiotic (zone of inhibition of ≥14 mm, as determined by standardized disk testing). Patients who had received antibiotics previously were included if the infecting organisms isolated just before teicoplanin therapy was begun were resistant to these drugs and if they had failed to respond to therapy, as attested to by clinical deterioration. We excluded from the study (i) patients with infections due not only to gram-positive organisms, (ii) patients with renal insufficiency (creatinine clearance rate, <50 ml/min), (iii) patients with a neutrophil count of <1,000 cells per mm3, (iv) pregnant or lactating females, and (v) moribund patients. Aerobic and anaerobic blood cultures were obtained from each patient before initiation of therapy. The criteria used for identifying bacteremia were positive blood cultures (at least two separate sets); all episodes were accompanied by fever, chills, or hypotension (blood pressure, <90 mm of Hg). Diagnosis of cellulitis or a soft-tissue infection required isolation of organisms from wound exudates, accompanied by evidence of soft-tissue infection (local inflammation, fever, chills, pain). Patients with osteomyelitis had either roentgenograms (five patients) or positive technetium and gallium bone scans (nine patients) which demonstrated evidence of bone infection before initiation of therapy; cultures were obtained by surgical drainage or needle aspiration.

The criteria used for pneumonia included (i) fever, sputum production, and leukocytosis, (ii) roentgenological evidence of an infiltrate, and (iii) isolation of pathogens from transtracheal aspirate, pleural fluid, or adequate expectorated sputum (Gram-stained smear showing ≥25 polymorphonuclear neutrophil leukocytes per low-power field with few or no squamous epithelial cells). Patients treated for septic thrombophlebitis had organisms isolated from the
catheter and blood 24 h after removal of the catheter, together with signs of infection (local pain, inflammation, fever, and chills).

Control cultures were obtained regularly during treatment (usually every 48 h) and at the end of therapy. Cultures were obtained during the posttreatment follow-up period if such cultures were clinically indicated and if suitable specimens were available.

The therapeutic efficacy of teicoplanin was evaluated by clinical and bacteriological criteria. Clinically, cure was regarded as complete resolution of the signs and symptoms of the patient due to the principal infection without relapse during the follow-up period (4 to 6 weeks for the majority of the patients); improvement was regarded as improvement of the signs and symptoms without complete cure; relapse applied to patients who presented again with the initial signs and symptoms during the follow-up period; and failure was defined as (i) lack of any favorable response or deterioration of clinical condition during teicoplanin therapy which required a subsequent change of the antimicrobial drug or (ii) death of the patient after a minimum of 48 h of therapy. Bacteriologically, success was considered according to whether eradication or persistence of the causative pathogen was observed. Superinfection was defined as the development of infection at the original site or at a new site during treatment or within the period of posttreatment follow-up, due to a pathogen which was not recognized as the original causative organism. Evaluation of the safety of teicoplanin in all patients included the following: complete blood count with differential, erythrocyte sedimentation rate, blood urea nitrogen, creatinine, liver function tests, and urine examination performed before, during, and after treatment.

Teicoplanin was supplied in 200-mg vials. The drug was dissolved in sterile water (3 ml/200 mg) and was administered either as a slow bolus (2-min) intravenous injection or intramuscularly. The concentrations of teicoplanin were measured in samples of serum obtained 1 h after completion of intravenous infusion and immediately before the start of the next dose. These measurements were performed on day 2 and were generally repeated at least once during the course of therapy. Values were measured by the standard agar well diffusion method, using Bacillus subtilis ATCC 6633 as the control strain (4).

Clinical isolates were identified by standard laboratory procedures (21). As a screening procedure, susceptibility testing was performed initially by the Kirby-Bauer method (2), using 30-μg disks, whereas MICs were subsequently determined by the standard tube dilution method in Mueller-Hinton broth with an inoculum of 10⁶ CFU/ml after dilution of an overnight culture (20). The MIC was defined as the lowest concentration of the antibiotic that prevented visible growth after incubation for 24 h. Bacteria were considered resistant to teicoplanin if the MIC was ≥3.1 μg/ml. Strains of *Staphylococcus aureus* were defined as resistant to methicillin if the MIC was ≥8 μg/ml. The susceptibility tests were performed at one of the participating centers.

## RESULTS

### Characteristics of the patients

The patients in this study were 31 males and 16 females whose ages ranged from 20 to 84 years (mean, 55.1 years); 11 of these patients had soft-tissue infections, 14 had bone and joint infections, 7 had endocarditis (4 acute and 3 subacute infections), 5 had pneumonia, 3 had septic thrombophlebitis, 3 had septicaemia of unknown origin, 2 had complicated urinary tract infections, 1 had a peritoneal shunt infection, and 1 had a perihepatic abscess. Overall, 24 patients were bacteremic. At the start of therapy, all patients were considered to be in either serious condition (33 patients) or fair condition (14 patients).

Underlying predisposing diseases or risk factors for infection were present in 37 patients and included extensive neoplastic disease (13 patients), cardiovascular disease (9 patients), joint prosthesis (2 patients), cardiac valve prosthesis (5 patients; 2 mitral and 3 aortic prosthetic cardiac valves), chronic obstructive lung disease (3 patients), polytrauma (3 patients), and diabetes mellitus (2 patients). All of the patients received a loading dose of 400 mg of teicoplanin on day 1; in 30 patients this was followed by a single daily 200-mg dose given intravenously. The remaining 17 patients received the drug intramuscularly for part or all of their therapy. Depending on the type of infection, the duration of treatment was between 4 and 71 days (mean, 22.1 days).

A total of 50 infecting organisms were isolated from the 47 patients given teicoplanin including 35 *Staphylococcus aureus* strains (including 8 methicillin-resistant *Staphylococcus aureus* strains), 4 *Staphylococcus epidermidis* strains, 4 *Streptococcus faecalis* strains, 2 *Streptococcus pneumoniae* strains, 1 *Streptococcus sanguis* strain, one *Streptococcus milleri* strain, one *Streptococcus pyogenes* strain, one *Streptococcus agalactiae* strain, and 1 *Micrococcus luteus* strain. As determined by disk diffusion susceptibility tests, an inhibitory zone of ≥14 mm was observed for all of the isolates tested. The exact MICs for the infecting pathogens are shown in Table 1.

### Clinical and bacteriological responses

Tables 2 and 3 show the clinical and bacteriological results. Clinically, 22 patients (46.8%) were cured, 8 patients (17.0%) improved, 2 patients (4.3%) relapsed after initial improvement, and 15 patients

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**TABLE 1. MICs of teicoplanin for infecting pathogens**

<table>
<thead>
<tr>
<th>Microorganism(s)</th>
<th>No. of isolates</th>
<th>MICs of isolates with a teicoplanin MIC of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>(methicillin susceptible)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>(methicillin resistant)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><em>Micrococcus luteus</em></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>Streptococcus faecalis</em></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><em>Other Streptococcus spp.</em></td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

*a* Streptococcus pneumoniae (two strains), *Streptococcus milleri* (one strain), *Streptococcus pyogenes* (one strain), *Streptococcus agalactiae* (one strain), and *Streptococcus sanguis* (one strain).
(31.9%) failed to respond to therapy, whereas bacteriologically the offending pathogen was eradicated in 25 patients (53.2%), 2 patients (4.3%) relapsed, and the bacteria persisted in 20 patients (42.5%). A total of 24 (51.1%) of the 47 patients were bacteremic. On the whole, 13 bacteremic patients (54.2%) were considered cured or improved at the completion of therapy. Details concerning the 11 failures in this group of patients are summarized in Table 4. In 6 of these patients the offending pathogen (Staphylococcus aureus in all cases) persisted in the blood for 3 to 8 days after therapy was begun and remained fully susceptible to teicoplanin.

In contrast with the bacteremic patients, 19 (82.6%) of the 23 nonbacteremic patients were cured or improved. This result is significantly better than the result achieved with bacteremic patients \((P = 0.037,\) as determined by the one-sided Fisher exact test). Among the four failures, three occurred in patients with postsurgery wound infections; one infection was due to Staphylococcus aureus after excision of a pretilial lipoma, one (also caused by Staphylococcus aureus) occurred after a laminectomy in a patient with cervical disk herniation, and one mixed infection (Staphylococcus epidermidis and Streptococcus faecalis) involved the stump of a leg in a patient with peripheral vascular disease. In the two latter patients, a diagnosis of osteitis was considered probable but could not be documented despite radiouclide scanning and roentgenographic studies. The fourth failure occurred in a patient suffering from generalized breast carcinoma who presented with acute suppurative arthritis (Staphylococcus aureus) of the wrist and of the interphalangeal joints of the hand.

Two patients who initially improved relapsed during the postsurgery follow-up period (Table 4, cases 11 and 12).

On the whole, five patients, of whom four were bacteremic, died during treatment. Three of these patients (Table 4, cases 5, 6, and 8) died from uncontrolled Staphylococcus aureus infections. In the other two patients, severe and rapidly progressive underlying illness (generalized carcinoma) contributed highly to death. Superinfection by gram-negative organisms occurred in six (12.8%) of the patients in this series. These episodes are summarized in Table 5.

**Serum levels.** The concentrations of teicoplanin in the sera of 41 patients were determined by using a bioassay on the second day of therapy. The mean peak level was 10.4 ± 5.3 μg/ml. The mean trough level was 2.7 ± 1.4 μg/ml. Serum levels were also determined in 23 patients during the course of therapy. While the mean peak levels remained similar (10.3 ± 4.7 μg/ml on day 5 and 10.4 ± 5.0 μg/ml on day 9), the mean trough levels slightly increased to 3.6 ± 1.4 and 3.9 ± 1.4 μg/ml after 5 and 9 days of therapy, respectively.

**Tolerance and adverse reactions.** Adverse reactions to teicoplanin were minor and reversible. These included mild thrombophlebitis (two patients), pain at the site of intramuscular injection (one patient), moderate pruritis (one patient), an allergic maculopapular rash that necessitated drug discontinuation (one patient), and mild and transient eosinophilia (two patients).

**DISCUSSION**

Teicoplanin, a novel glycopeptide antibiotic that is related to vancomycin, exhibits potent in vitro activity against virtually all gram-positive bacteria, including Streptococcus faecalis and Staphylococcus aureus (beta-lactamase producers, as well as methicillin-resistant Staphylococcus aureus strains) (3, 7, 8, 10, 11, 14, 18, 19). Studies with animal models have indicated that teicoplanin is at least as effective as vancomycin in curing experimental septicemia or endocarditis caused by gram-positive bacteria (5, 14). So far, no data have been reported on the efficacy and safety of this drug in serious gram-positive infections. In the present study, teicoplanin was effective in a variety of infections, with an overall clinical response rate of 63.8% and eradication of the causative organism in 53.2% of the cases (determined after posttreatment follow-up for a minimum of 4 weeks).

Our results are quite similar to those obtained by Klustersky et al. (12), who evaluated the effectiveness of vancomycin in severe infections caused by methicillin-resistant Staphylococcus aureus and found a favorable response rate in 16 (59.2%) of 27 patients. Other investigators have reported higher cure rates (from 74 to 86%) with vancomycin in the treatment of bacteremia caused by methicillin-resistant Staphylococcus aureus (6, 13, 16).
crepancies in the results might be partially explained by taking into account the underlying illnesses of the patients, the more or less late onset of therapy, and the assessment of the outcome in terms of survival rather than simply by clearing of the bacteremia.

When analysis of our results was focused on Staphylococcus aureus bacteremias, a favorable outcome was achieved in only 8 of 17 patients (47.0%); 4 of the 9 failures were rapidly fatal. In our study nonbacteremic patients were cured or improved in 82.6% of the cases (taking into account all gram-positive cocal infections), reflecting perhaps the less severe underlying diseases in this group of patients. Also striking in this study was the occurrence of superinfections due to gram-negative bacteria in 6 patients (12.8%). These superinfections were probably related to the narrow antibacterial spectrum of teicoplanin, which is limited to gram-positive bacteria.

When the bacteriological outcome is considered, it appears that persistence or recurrence of the pathogen was a frequent complication of therapy with teicoplanin. This could be attributed to an undrained focus in only five patients. Indeed, persistence of the pathogen had a major role in the failures which we observed in six of nine patients with Staphylococcus aureus septicemia. Undertreatment could not account for these failures since the serum levels in these patients always exceeded the MIC (mostly by 10 to 50 times) of the offending Staphylococcus aureus strain and since no difference could be found between the mean peak and trough serum levels in the patients who responded to teicoplanin (10.9 ± 5.1 and 3.5 ± 1.2 μg/ml) and in the patients who failed to do so (9.9 ± 5.8 and 3.2 ± 1.6 μg/ml). Moreover, none of the strains isolated demonstrated tolerance to teicoplanin, and their MBCs never exceeded more than four times their MICs. It might also be speculated that teicoplanin has a relatively weak and slow bactericidal activity in vivo, thus explaining the persistence of bacteria in blood cultures during treatment. This was clearly shown in a cross-over study performed by Lagast et al. (H. Lagast, M. Husson, and J. Klastersky, Program Abstr. 24th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 582, 1984), who compared the bactericidal activities of teicoplanin and vancomycin in the sera of six volunteers after intravenous

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Underlying Illness</th>
<th>Infection</th>
<th>Organism</th>
<th>MIC (μg/ml)</th>
<th>Duration of Therapy (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>Mitral valve prosthesis</td>
<td>Endocarditis</td>
<td>Micrococcus luteus</td>
<td>0.1</td>
<td>49</td>
<td>Recurrence of septicemia after 43 days; favorable evolution after replacement of the prosthesis</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>Prostatic carcinoma</td>
<td>Postnephrostomy urinary tract infection</td>
<td>Staphylococcus aureus</td>
<td>0.2</td>
<td>7</td>
<td>No clinical improvement; persistence of pathogen; patient died after 8 days</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>Rectal carcinoma</td>
<td>Perineal wound</td>
<td>Staphylococcus aureus (methicillin resistant)</td>
<td>0.2</td>
<td>11</td>
<td>Recurrent septicemia after 3 months</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>Aortic valve prosthesis</td>
<td>Endocarditis</td>
<td>Staphylococcus aureus</td>
<td>1.6</td>
<td>4</td>
<td>Blood cultures remained positive after 4 days; patient died from infection after 3 months</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>Coronary artery bypass graft</td>
<td>Mediastinitis poststernotomy</td>
<td>Staphylococcus aureus</td>
<td>0.05</td>
<td>10</td>
<td>Blood cultures remained positive after 8 days; subsequent superinfection of the wound with Serratia marcescens; patient died after 10 days</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>Pancreatic carcinoma</td>
<td>Pneumonia</td>
<td>Staphylococcus aureus (methicillin resistant)</td>
<td>0.2</td>
<td>5</td>
<td>Blood cultures and bronchial aspirates remained positive after 5 days; patient died on the same day</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>Thyroid cancer</td>
<td>Septicemia</td>
<td>Staphylococcus aureus</td>
<td>0.05</td>
<td>12</td>
<td>Persistence of temperature and absence of clinical improvement after 12 days of therapy, despite negative blood cultures</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>Peripheral vascular disease</td>
<td>Septicemia, bladder catheter-related urinary tract infection</td>
<td>Staphylococcus aureus</td>
<td>0.05</td>
<td>8</td>
<td>Infection progressed despite subsequent negative blood cultures; patient died after 9 days</td>
</tr>
<tr>
<td>9</td>
<td>64</td>
<td>Diabetes mellitus</td>
<td>Septic thrombophlebitis</td>
<td>Staphylococcus aureus</td>
<td>0.2</td>
<td>7</td>
<td>Persistent blood cultures on day 5; favorable evolution after drainage of a subcutaneous abscess</td>
</tr>
<tr>
<td>10</td>
<td>22</td>
<td>Drug addict</td>
<td>Tricuspid endocarditis</td>
<td>Staphylococcus aureus (methicillin resistant)</td>
<td>0.2</td>
<td>7</td>
<td>Blood cultures positive after 6 days; patient recovered after surgery</td>
</tr>
<tr>
<td>11</td>
<td>64</td>
<td>Thyoma decubitus ulcer</td>
<td>Septic thrombophlebitis</td>
<td>Staphylococcus epidermidis</td>
<td>1.6</td>
<td>8</td>
<td>Breakthrough bacteremia due to Bacteroides thetaiotaomicron on day 4; patient died on day 6</td>
</tr>
<tr>
<td>12</td>
<td>72</td>
<td>Aortic valve prostl. sis</td>
<td>Endocarditis</td>
<td>Staphylococcus faecalis</td>
<td>0.4</td>
<td>42</td>
<td>Relapse 13 weeks after end of therapy</td>
</tr>
<tr>
<td>13</td>
<td>61</td>
<td>Chronic osteomyelitis</td>
<td>Staphylococcus aureus</td>
<td>Staphylococcus aureus</td>
<td>0.2</td>
<td>5</td>
<td>Relapse after 6 weeks despite surgical ablation of necrotic tissues</td>
</tr>
</tbody>
</table>
administration of 200 mg of teicoplanin and 1 g of vancomycin. These authors found that the killing effect of twofold-diluted, pooled sera on five strains of *Staphylococcus aureus* at concentrations of 10⁶ CFU/ml was markedly lower in the group which received teicoplanin, especially when they considered the antibacterial activity during the first 6 hours of incubation (less than a 1-log decrease in the number of colony-forming units per milliliter for teicoplanin, while vancomycin produced a 4-log reduction).

Teicoplanin was tolerated well by patients even when it was given intramuscularly for as long as 4 weeks (seven patients). No serious side effects were noticed. Only one patient developed allergic purpura, which required the discontinuation of therapy on day 16. Interestingly, we did not observe any alteration of the renal function in this series. Vancomycin, on the other hand, has been associated occasionally with nephrotoxicity (9). Moreover, because of its pharmacokinetics, which allows a single daily dose, teicoplanin appears to be a suitable alternative to other drugs for long-term treatment of chronic infections.

Based on the results of this study, we conclude that teicoplanin has potential efficacy, at least in nonbacteremic gram-positive coccus infections, including infections caused by methicillin-resistant *Staphylococcus aureus* strains. Controlled trials are now needed to compare the efficacy of teicoplanin with that of vancomycin. Improvement of the effectiveness of teicoplanin in serious *Staphylococcus aureus* infections, especially in debilitated patients, might require its use in combination with bactericidal drugs, such as rifampin or gentamicin (17).

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**LITERATURE CITED**


CLINICAL EVALUATION OF TEICOPLANIN


