Clinical Evaluation of Efficacy, Pharmacokinetics, and Safety of Teicoplanin for Serious Gram-Positive Infections

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Nineteen patients hospitalized for serious gram-positive infections were treated with teicoplanin, a new glycopeptide antibiotic. A variety of infections were treated, including endocarditis, septic thrombophlebitis, osteomyelitis, pyogenic arthritis, and soft tissue infection. Of 13 infections that could be evaluated in 12 patients, there were 8 clinical cures, 2 improvements, 1 recurrence, and 2 failures. Of the eight patients with Staphylococcus aureus bacteremia, seven were clinically cured or improved with teicoplanin therapy. Of the nine patients in whom the bacteriological response to treatment could be fully evaluated, six were cured; there was recurrence of infection in one, and treatment failed in two patients. In vitro testing showed the 13 bacterial isolates (9 S. aureus, 3 S. epidermidis, and 1 group B streptococcus) to be uniformly susceptible to teicoplanin, with MICs ranging from 0.12 to 0.5 μg/ml. Every isolate was more susceptible in vitro to teicoplanin than to vancomycin. Three of the staphylococcal isolates were resistant to methicillin. Pharmacokinetic studies demonstrated that after an initial drug-accumulation period, a single daily dose adequately maintained the teicoplanin concentrations in serum within therapeutic ranges. Teicoplanin also penetrated well into synovial fluid. The drug was well tolerated by either intravenous or intramuscular administration. The most significant adverse reaction was an urticarial rash which required discontinuation of therapy in one patient; a second patient experienced a modest decrease in high-frequency auditory threshold. Asymptomatic eosinophilia and mild elevation of serum transaminases were noted as well. The results of this study suggest that teicoplanin is a safe and effective new agent for treatment of serious infections caused by gram-positive organisms.

Teicoplanin is a new glycopeptide antibiotic structurally related to vancomycin and ristocetin. Like vancomycin, it is highly active in vitro against a wide spectrum of gram-positive organisms, including enterococci and both methicillin-susceptible and methicillin-resistant staphylococci (3, 14, 21). Unlike vancomycin, however, teicoplanin has a long elimination half-life permitting administration once a day (11, 20, 21), and it is well tolerated when given intramuscularly (i.m.), with a bioavailability of 90% (21). These pharmacokinetic properties suggest that teicoplanin may provide an antimicrobial alternative for treatment of serious gram-positive infections in patients who have limited venous access or hypersensitivity to β-lactam antibiotics. We present the results of an open study of the efficacy, pharmacokinetics, and safety of teicoplanin in patients hospitalized for staphylococcal and streptococcal infections.

MATERIALS AND METHODS

Patient enrollment. Hospitalized patients 18 years of age or older with suspected or established infections caused by gram-positive organisms and who required treatment with parenteral antibiotics were entered in the study after giving written informed consent. Teicoplanin was discontinued after 72 h if pretreatment cultures failed to yield a susceptible pathogen. Although an aminoglycoside could be given empirically during the initial 24 h, patients who had received prior antibiotic therapy or who were likely to require additional antimicrobial drugs beyond day 1 were excluded. Patients also were excluded for previous allergic reactions to vancomycin or underlying chronic renal or hepatic dysfunction. Women of child-bearing potential were required to have a negative pregnancy test before enrollment. The study protocol was approved by the Human Research Committees for both the University of Cincinnati College of Medicine and the Cincinnati Veterans Administration Medical Center.

Clinical criteria for infections. Bacteremia was defined by fever, chills, or hypotension and the isolation of a pathogenic organism from at least two pretreatment blood cultures. Septic thrombophlebitis was diagnosed in patients with a suggestive physical examination in conjunction with bacteremia and documentation of an intravenous thrombus by impedance plethysmography, venography, or computerized tomography. Endocarditis was diagnosed in patients who had bacteremia together with a new or changing heart murmur, a valvular vegetation demonstrated by echocardiography, or septic pulmonary emboli in the absence of any other apparent endovascular infection. Pneumonia was diagnosed if a chest radiograph revealed a pulmonary infiltrate. The diagnosis of soft tissue, bone, or joint infection required an appropriate examination and compatible radiographic studies plus bacteremia or a positive culture obtained by direct closed-space needle aspiration of the infected tissue.

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The efficacy of teicoplanin was assessed by both clinical and bacteriological criteria. Patients were considered to be cured clinically if signs and symptoms of infection were eradicated at the end of treatment. Clinical improvement was defined as a definite reduction in signs and symptoms during the study period but incomplete resolution of infection. Clinical recurrence was defined as an initial eradication of signs and symptoms with a subsequent worsening of the clinical condition caused by infection after termination of therapy. Patients were judged to have failed therapy if they had an inadequate clinical response. Bacteriological cure was defined as the elimination of the causative organism from cultures during and after therapy. Patients who had a complete clinical resolution of infection so that follow-up culture was impossible, as for soft tissue, bone, and joint infections, were also judged to have been cured bacteriologically. Bacteriological failure was defined as the persistence of the initial pathogen during treatment. Patients were considered to have bacteriological recurrence if the causative pathogen was absent from cultures obtained at the completion of therapy but reappeared at the same site during follow-up observation. The bacteriological response could not be evaluated for bacteremic patients from whom posttreatment specimens were not obtained or who received additional antibiotics after teicoplanin was discontinued.

Monitoring for toxicity. All patients were monitored daily by the infectious disease consultation service. The following tests were done before therapy, at weekly intervals during therapy, and after discontinuation of teicoplanin: (i) complete blood count with differential leukocyte and platelet counts, (ii) determination of serum electrolytes and glucose, (iii) renal and hepatic function, (iv) urinalysis, and (v) prothrombin time and activated partial thromboplastin time. Base-line audiometric testing was performed and repeated weekly after day 10 and at the completion of therapy.

Drug administration. Teicoplanin was reconstituted in 50 ml of normal saline and infused intravenously (i.v.) over 30 min once every 24 h. Patients received a loading dose of 400 or 600 mg followed by daily maintenance doses of 200, 400, or 600 mg. Depending on the severity of infection and the response to therapy, the daily dose was adjusted to achieve a peak concentration in serum between 25 and 40 µg/ml and a trough concentration in serum between 5 and 15 µg/ml. For patients with poor venous access, teicoplanin was reconstituted as a solution of 200 mg/3 ml of saline and administered in one or two 200-mg doses once daily by deep i.m. injection. Patients who complained of pain on injection received subsequent doses reconstituted in a 1% lidocaine solution. The duration of treatment varied with the type of infection treated and the clinical and bacteriological response to therapy.

Antibiotic concentration assay. Venous blood was collected 30 min after i.v. infusion and 2 h after i.m. injection for determination of the peak concentration of teicoplanin in serum. Blood for determination of trough concentration was obtained before the next dose (18 to 24 h after administration). When present, gentamicin was removed by adsorption with cellulose phosphate. The determinations of teicoplanin levels in both serum and synovial fluid were done by using a modification of the disk diffusion bioassay technique for vancomycin as described by Walker and Kopp (22) using buffered glucose minimal salts medium and a Bacillus subtilis ATCC 6633 spore suspension (Difco Laboratories, Detroit, Mich.) as the indicator organism. All assays were run in quadruplicate.

Antimicrobial susceptibility testing. Determinations of teicoplanin and vancomycin MICs were performed with macroscopic tube dilution assays in cation-supplemented Mueller-Hinton broth (Difco) according to National Committee for Clinical Laboratory Standards guidelines (12). The MBC was determined to be the lowest dilution of the drug which effected 99.9% killing after 48 h of incubation. Staphylococci were tested for resistance to methicillin by using the National Committee for Clinical Laboratory Standards-recommended agar disk diffusion procedure using Mueller-Hinton agar and a 1-µg oxacillin disk (13). After incubation at 30°C for 24 h, isolates with inhibition zone diameters of 11 mm or less were considered to be methicillin resistant.

RESULTS

Nineteen patients were enrolled in the study, and all were included in the analysis of pharmacokinetic and toxicity data. Teicoplanin was discontinued in five patients whose pretreatment cultures failed to grow a pathogenic organism and in a sixth patient whose blood cultures repeatedly yielded a Fusobacterium species presumed to be resistant to the study drug. A seventh patient was entered in the study for pneumococcal pneumonia; however, in the hospital he had repeated aspiration of oropharyngeal secretions, and he died on hospital day 8 from progressive respiratory failure and massive upper gastrointestinal bleeding. Premortem sputum cultures grew abundant Haemophilus influenzae resistant to teicoplanin. These seven patients were excluded from evaluation of drug efficacy.

Clinical efficacy. The 12 patients who could be evaluated fell into two groups. Nine intravenous drug abusers had a mean age of 31 years (range, 20 to 55 years) and were otherwise healthy. The remaining three patients had a mean age of 64 years (range, 59 to 72 years), and all three had underlying disease: one had refractory sideroblastic anemia requiring biweekly blood transfusion through a permanent indwelling central venous catheter, one had laryngeal carcinoma, and was ventilator dependent in the intensive care unit, and one had had a recent cervical laminectomy. Three patients who could be evaluated each received two doses of gentamicin during the first 24 h, in addition to teicoplanin.

The 12 patients had 13 infections (Table 1). Bacteremia, present in eight of the nine drug abusers, was the most common infection treated and arose from an identifiable primary focus in all but one instance. The ninth drug abuser had pyogenic arthritis but was not bacteremic. Two patients were considered to have only catheter-associated infections when paired blood cultures drawn through the catheter but not from a peripheral vein were positive. Each of these two patients had an associated soft tissue infection. The final patient had postoperative cervical osteomyelitis.

Staphylococcus aureus was the most frequent pathogen and was cultured from the blood or synovial fluid of all nine drug abusers. One addict with endocarditis had group B streptococcal bacteraemia as well. Staphylococcus epidermidis was recovered from the blood of both patients with catheter-associated infection and from needle aspiration of the cervical spine in the patient with osteomyelitis.

The teicoplanin MICs for the nine S. aureus and three S. epidermidis isolates ranged from 0.12 to 0.5 µg/ml. In every case, the teicoplanin MIC was at least twofold lower than the corresponding vancomycin MIC. The teicoplanin MBC was within 3 dilutions of the corresponding MIC for each of the staphylococcal isolates. On the other hand, the MBCs of teicoplanin and vancomycin for the group B streptococcus exceeded the corresponding MIC by 128 and 16 times,
respectively. One of the *S. aureus* isolates and two of the *S. epidermidis* isolates were resistant to oxacillin by the disk diffusion method.

Overall data on the outcome of teicoplanin therapy for the 13 infections treated revealed 8 clinical cures, 2 improvements, 1 recurrence, and 2 failures (Table 1). Bacteriologically, there were six cures, one recurrence, and two failures: the bacteriological response could not be evaluated in four patients (two did not have follow-up blood cultures but were clinically well on examination 6 weeks after treatment, and two were improved clinically on teicoplanin but subsequently received additional antibiotics). Both patients with catheter-associated infections were cured clinically and bacteriologically. The first patient had an infected arterial catheter removed and an overlying abscess drained; the second patient was successfully treated with teicoplanin alone without removal of the infected permanent central venous catheter. The patient with postoperative cervical osteomyelitis also was cured clinically and bacteriologically.

Therapy for septic arthritis failed in one of two patients. A 32-year-old drug abuser admitted for staphylococcal arthritis of the hip underwent open surgical debridement. She defervesced on teicoplanin by hospital day 4 but had persistent pain, leukocytosis, and purulent hip drainage that remained culture positive for *S. aureus* after 6 days of teicoplanin therapy. Nafcillin was substituted on day 7 with a complete clinical response.

Four of the eight bacteremic intravenous drug abusers were cured clinically with teicoplanin. Another patient had recurrent bacteremia after apparent cure of pyogenic sacroiliitis caused by methicillin-resistant *S. aureus*. Although reinfection resulting from continued drug abuse or discharge seemed the most likely explanation, relapse of incompletely treated endocarditis could not be excluded.

Two additional patients with staphylococcal tricuspid endocarditis were improving clinically on teicoplanin before their antibiotic therapy was altered. One patient had a prompt clinical response but developed urticaria and recurrent fever following teicoplanin dose 8; therapy was successfully completed with nafcillin. Nafcillin was substituted for teicoplanin in the other patient on hospital day 13 because of an apparent failure to respond; however, blood cultures had become sterile, and the patient had defervesced the morning of the change in treatment.

Teicoplanin therapy failed in the final bacteremic drug abuser, a patient with staphylococcal tricuspid endocarditis complicated by extensive bilateral cavitary pneumonia, perivascular cellulitis of the thigh, cutaneous emboli, and immune-complex synovitis. Because of persistent bacteremia, nafcillin was substituted for teicoplanin on hospital day 7. Subsequent blood cultures were sterile; however, the patient continued to have spiking fever and chills. On day 18 nafcillin was discontinued, and therapy was successfully completed with vancomycin and rifampin for an additional 25 days. Fever persisted until day 27 of treatment.

The temporal response to therapy varied widely among the seven patients with staphylococcal bacteremia who were clinically cured or improved by teicoplanin. The mean duration of bacteremia was 4.6 days (range, 1 to 10 days), and body temperature exceeded 38°C for a mean of 6.6 days (range 1 to 12 days). Among the five patients who presented with leukocytosis and who had serial blood-count determinations, the leukocyte count remained greater than 10,000/mm³ for a mean of 8.6 days (range, 2 to 18 days).

**Pharmacokinetics.** Teicoplanin therapy was initiated with a variety of loading-dose regimens ranging from 400 to 600 mg given i.v. or i.m. Of 17 patients, 13 had peak concentrations in serum measured after the first i.v. infusion (Table 2). For those receiving less than 7 mg/kg of body weight, the mean peak concentration in serum was 16 μg/ml, and five of six patients had levels lower than 20 μg/ml. For those receiving more than 7 mg/kg, the mean peak concentration in serum was 27 μg/ml, and five of six had peak levels greater than 20 μg/ml.

Teicoplanin concentrations in serum were obtained approximately halfway through the first dosing interval in five patients. Four of the five levels were lower than 7 μg/ml. Trough concentrations measured after the loading dose were

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### TABLE 1. Clinical and bacteriological outcome of teicoplanin therapy for 12 patients

<table>
<thead>
<tr>
<th>Bacteremia</th>
<th>Clinical response</th>
<th>Bacteriological response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cure</td>
<td>Improvement</td>
</tr>
<tr>
<td>Endocarditis (4)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Septic thrombophlebitis (2)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Septic arthritis (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No apparent focus (1)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Arthritis (2)*</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Catheter-associated infection (2)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Osteomyelitis (1)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* One patient had both arthritis and bacteremia; each infection had a different outcome.

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### TABLE 2. Teicoplanin concentrations in serum after various loading-dose regimens

<table>
<thead>
<tr>
<th>Loading dose (mg/kg of body wt) (no. of patients)</th>
<th>Mean concn in serum (μg/ml) (range)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak</td>
</tr>
<tr>
<td>&lt;7 mg/kg i.v. b (9)</td>
<td>16 (11–27) (6 samples)</td>
</tr>
<tr>
<td>&gt;7 mg/kg i.v. a (8)</td>
<td>27 (18–44) (6 samples)</td>
</tr>
<tr>
<td>8 mg/kg i.m. b (2)</td>
<td>7.8 (1 sample)</td>
</tr>
</tbody>
</table>

* Serum for peak concentrations was obtained 30 min after the completion of an i.v. infusion or 2 h after an i.m. injection. Serum for middose and trough concentrations was obtained from 9 to 14 h and from 18 to 24 h after the dose, respectively.

a i.v. infusion took place over 30 min.
TABLE 3. Steady-state concentrations of teicoplanin in serum with various maintenance-dose regimens

<table>
<thead>
<tr>
<th>Maintenance dose (mg/kg body w. no. of patients)</th>
<th>Mean concn in serum (μg/ml) (range) [n]</th>
<th>Peak</th>
<th>Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 mg/kg i.v. a (5)</td>
<td>16 (8.8-36) [8]</td>
<td>4.1 [1]</td>
<td></td>
</tr>
<tr>
<td>≥4 mg/kg i.v. b (6)</td>
<td>26 (34-20) [35]</td>
<td>10.5 (6.8-18) [14]</td>
<td></td>
</tr>
<tr>
<td>&gt;4 mg/kg i.m. (4)</td>
<td>14 (6.7-22) [18]</td>
<td>11.1 (9-15) [10]</td>
<td></td>
</tr>
</tbody>
</table>

a Serum for peak concentrations was obtained 30 min after the completion of an i.v. infusion or 2 h after an i.m. injection. Serum for trough concentrations was obtained 24 h later. All peak concentrations after maintenance doses are represented, but only trough concentrations obtained after doses given on day 6 or later are shown to eliminate the equilibration period. n, Number of serum samples available.

b i.v. infusion took place over 30 min.

The teicoplanin concentrations in serum during maintenance therapy are shown in Table 3. Peak concentrations in serum were higher with larger doses, but there was no relationship between the duration of therapy and peak concentrations, which remained stable on a constant dose. The mean peak concentration in serum was 26 μg/ml for patients receiving more than 4 mg/kg per day i.v., in contrast to lower peak levels achieved in patients receiving i.m. or smaller i.v. doses.

Serial data for trough teicoplanin concentrations in serum were available from periods when nine patients received a constant maintenance dose. Before stabilizing, trough levels accumulated over a variable period of at least 5 days, during which the average daily increment in concentration was 40% (range, 18 to 63%). Mean trough concentrations after equilibration were 10 to 11 μg/ml in 10 patients who received more than 4 mg/kg per day either i.v. or i.m. (Table 3). In one patient with normal renal function, teicoplanin concentrations in serum were 16, 9, 5.8, and 4.5 μg/ml at 2, 24, 48, and 72, respectively, after the last dose on day 28. These values are consistent with an elimination half-life of more than 24 h.

Teicoplanin concentrations were determined in the synovial fluid of two patients. Two hours after a 600-mg i.v. loading dose, a level of 7.2 μg/ml was measured in the purulent fluid from an infected hip in one patient. Serial specimens were obtained in a second patient who had immune-complex synovitis of the knee. Although joint fluid accumulation appeared to be less rapid than serum accumulation, within 24 h the teicoplanin concentration in the synovial fluid was 11.0 μg/ml and exceeded 35% of the simultaneous concentration in serum.

Side effects. Although all 19 patients enrolled were monitored for drug toxicity, the 7 patients excluded from analysis of efficacy received a limited number of doses and had no side effects. The 12 patients who could be evaluated had a mean duration of teicoplanin therapy of 18.5 days (range, 6 to 42 days) and received a mean total dose of 7,000 mg (range, 1,800 to 17,000 mg). Of the 12 patients, 7 had at least one possible drug-related adverse effect. However, teicoplanin was discontinued because of suspected drug toxicity in only one patient (described above) who developed an urticarial skin eruption on day 8 of therapy. Three patients had a three- to fivefold increase in serum transaminases during treatment. In no case did the values exceed three times the upper limit of the normal range, and no patient had symptoms of hepatitis. The transaminases returned to normal after therapy. Eosinophilia (total eosinophil count, >450/mm³) was noted in an additional three patients, none of whom had any other allergic phenomena, such as rash, drug fever, or interstitial nephritis.

Serial bedside audiograms were obtained from 10 of the 13 patients who received more than 2 days of teicoplanin therapy. Background noise may have biased the test results. Nine patients had stable or improved hearing during treatment, but one patient experienced a reproducible 20- to 30-dB decrease in auditory threshold over the high-frequency range in both ears. She received a total teicoplanin dose of 3,000 mg over 7 days; measured teicoplanin concentrations in serum never exceeded 10 μg/ml. Audiograms were normal before therapy and on day 6 but were abnormal on days 12 and 22.

Teicoplanin administration was well tolerated by both the i.v. and i.m. routes. Six patients received a total of 135 i.m. injections; most noted mild local pain which resolved when teicoplanin was reconstituted in a 1% lidocaine solution. There were no episodes of phlebitis after i.v. infusion or sterile abscess after i.m. administration. No patient developed hypotension or a flushing reaction while receiving the drug.

**DISCUSSION**

Based on the results of this study, teicoplanin appears to be an effective new antibiotic for the therapy of serious staphylococcal disease. Of the 13 infections treated, 8 were cured clinically and 2 were improving when teicoplanin was discontinued. An additional patient with recurrent staphylococcal bacteremia most likely was cured of his infection as well, only to become reinfected as a result of continued i.v. narcotic abuse. Moreover, the 12 patients had a variety of severe infections. There were eight episodes of bacteremia, arising from a deep-seated focus of infection in seven cases. Three patients were treated for bone or joint infections.

Staphylococcal endovascular infection is common among i.v. drug abusers and generally carries a good prognosis (17). The clinical response of our eight bacteremic patients to teicoplanin therapy echoes this published experience: four were cured, one had recurrent bacteremia after an apparent initial cure, and two had clearly improved when teicoplanin was discontinued. Furthermore, the temporal response to teicoplanin therapy also compares favorably to that reported with other antistaphylococcal regimens (1, 9, 16). For example, the mean duration of bacteremia and median duration of fever and leukocytosis (3.4, 7, and 11 days, respectively) reported by The National Collaborative Endocarditis Study Group for drug abusers treated with nafcillin alone (8) are quite similar to our findings with teicoplanin.

The occasionally refractory response to treatment of complicated staphylococcal endocarditis is illustrated by the only bacteremic patient who unequivocally failed teicoplanin
therapy. This patient remained bacteremic for 6 days and febrile for 27 days despite sequential therapy with teicoplanin, nafcillin, and, finally, vancomycin plus rifampin. A similarly protracted course has been well documented in many other patients treated with conventional antistaphylococcal antibiotics (5, 10, 15, 18, 23).

There has been one other published report on the clinical efficacy of teicoplanin. Glupczynski and colleagues (6) studied 47 patients with a variety of serious gram-positive infections. Although 83% of the 23 patients with non-bacteremic infections were cured or improved with teicoplanin, only 54% of 24 bacteremic patients had a clinical response. In particular, a favorable outcome was achieved in just 8 of 17 patients with S. aureus bacteremia; 4 of the 9 failures were rapidly fatal.

Several factors may account partially for the discrepancy in the response of staphylococcal bacteremia to teicoplanin therapy between this early report (6) and the present study. The bacteremic patients enrolled in our study were otherwise healthy young i.v. drug abusers. In contrast, those studied by Glupczynski and co-workers were older patients with serious underlying disease, including carcinoma, and prosthetic heart valves. The markedly worse prognosis of staphylococcal endocarditis in the nonaddict population is well-known (2). In addition, patients received a daily 200-mg teicoplanin maintenance dose in the previous study, whereas the daily maintenance dose was at least 400 mg in seven of eight bacteremic patients in our study. Although Glupczynski et al. noted no difference in the peak teicoplanin concentration in serum between the bacteremic patients who responded to therapy and those who failed, the mean peak teicoplanin concentration in serum that these patients achieved (10.4 μg/ml) was nevertheless significantly lower than that achieved in our bacteremic patients (26 μg/ml).

The results of in vitro susceptibility testing for the 13 isolates in this study are in accord with those reported by other investigators. Typical MICs are ≤0.8 μg/ml for most S. aureus isolates and ≤1.6 μg/ml for most S. epidermidis isolates, regardless of methicillin susceptibility (3, 14, 21). Every isolate was more susceptible in vitro to teicoplanin than to vancomycin.

The serial pharmacokinetic data we obtained in patients with serious infections expand the teicoplanin pharmacokinetic profile generated by previous investigators in studies of single-dose administration using healthy volunteers (11, 20, 21). Although teicoplanin dosage was not based on body weight in this study, those who received an initial loading dose of at least 7 mg/kg i.v. had a mean peak concentration of 27 μg/ml in serum. This value is similar to that measured by Verbist et al. (21) after a 6-mg/kg dose and by McNulty et al. (11) after a mean dose of 5.7 mg/kg. However, as expected with a drug given once daily, at least 5 days were required to reach steady-state levels. Our results demonstrated that during a significant portion of day 1, the teicoplanin concentrations in serum were below the desired range. After a loading dose and period of initial accumulation, a single daily dose adequately maintained the concentrations of teicoplanin in serum within acceptable ranges.

On the basis of the pharmacokinetic data from this and earlier studies (11, 20, 21), we can now offer preliminary teicoplanin dosage guidelines. Because the first few days of therapy are the most important when treating patients with septicemia, it seems prudent to shorten the time needed to reach steady state. We therefore recommend that teicoplanin therapy begin with three i.v. doses of 6 to 7 mg/kg at 12-h intervals, followed by single daily doses of the same amount. The teicoplanin concentrations in serum should be monitored thereafter, with daily doses adjusted to maintain trough concentrations of approximately 10 μg/ml.

Previous pharmacokinetic studies have also suggested that teicoplanin has excellent tissue penetration (20, 21). This prediction has been confirmed for skin blister fluid in human subjects (11) and for cerebrospinal fluid in a rabbit model of experimental meningitis (D. D. Lee, R. Maseraati, and W. M. Scheld, Program Abstr. 25th Intersef. Conf. Antimicrob. Agents Chemother., abstr. no. 689, 1985). We have now documented concentrations of teicoplanin in synovial fluid many times higher than the expected MIC for most gram-positive organisms.

Teicoplanin administration was well tolerated in this study. There were no episodes of catheter-associated phlebitis even during prolonged i.v. therapy, in contrast to vancomycin administration, with which phlebitis is common (4, 19). Likewise, i.m. administration was uncomplicated and accepted well by patients.

The most significant adverse reaction to teicoplanin in this study was an urticarial rash which required discontinuation of therapy in one patient. Another potentially serious side effect, an asymptomatic but reproducible 20- to 30-dB decrease in high-frequency auditory threshold, occurred in one patient 1 week after teicoplanin was discontinued even though the duration of therapy was short and the teicoplanin concentration in serum was low. As in this study, pruritus, rash, eosinophilia, and transaminase elevation have been reported occasionally in other preliminary clinical investigations with teicoplanin (6); J. Kosmidis and S. Kastanakis, Abstr. 4th Medit. Congr. Chemother., abstr. no. 349, 1984; Y. N. Van Laethem, H. Goossens, S. Cran, J. P. Butzler, and N. Clumeck, 24th ICAAC, abstr. no. 1219, 1984). Determination of the clinical significance of these apparently minor adverse reactions must await further testing in a large number of patients.

In conclusion, teicoplanin appears to be a safe and efficacious new agent for the treatment of serious staphylococcal infections. Its pharmacokinetic properties and greater in vitro activity suggest that it may provide an alternative to vancomycin in patients with hypersensitivity to β-lactam antibiotics or with infections caused by methicillin-resistant organisms. Teicoplanin may be particularly useful for treating gram-positive infections in parenteral drug abusers, because these patients often have limited venous access. Teicoplanin also penetrates well into synovial fluid. It may therefore become a therapeutic option for patients with gram-positive arthritis, especially those with prosthetic joint infection in which coagulase-negative staphylococci have become the predominant pathogen (7). These organisms are often resistant to β-lactam antibiotics, and teicoplanin lends itself to prolonged outpatient parenteral therapy because of its potential for i.m. administration once a day. Further evaluation of the clinical efficacy of teicoplanin in comparison to vancomycin and antistaphylococcal β-lactams therefore is warranted.

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LITERATURE CITED


