Prospective Study of Oral Teicoplanin versus Oral Vancomycin for Therapy of Pseudomembranous Colitis and *Clostridium difficile*-Associated Diarrhea

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Received 17 January 1992/Accepted 13 July 1992

A prospective, randomized study comparing oral teicoplanin with oral vancomycin in the treatment of pseudomembranous colitis (PMC) and *Clostridium difficile*-associated diarrhea (CDAD) was performed. Teicoplanin was administered at a dosage of 100 mg twice a day for 10 days, and vancomycin was administered at a dosage of 500 mg four times a day for 10 days. CDAD was diagnosed by demonstrating both *C. difficile* and cytotoxin in the feces of symptomatic patients (more than three loose stools per day). The diagnosis of PMC was also based on colonoscopy. Cytotoxin assay and cultures were checked in all patients 7 to 10 days after discontinuation of therapy and 25 to 30 days thereafter. Of the 51 patients enrolled, 46 were judged to be assessable. Among these, 26 received teicoplanin and 20 received vancomycin. At enrollment, both groups were comparable in terms of age, sex, occurrence of PMC or CDAD, and previous antibiotic treatment. Eighteen of the 20 patients in the vancomycin group and 10 of the 26 patients in the teicoplanin group had previous undergone surgery (\(P = 0.0004\)). Treatment resulted in the clinical cure of 20 (100%) vancomycin and 25 (96.2%) teicoplanin patients (\(P = 0.56\)). After discontinuation of therapy, clinical symptoms occurred in four (20%) vancomycin patients and two (7.7%) teicoplanin patients (\(P = 0.21\)). Posttherapy asymptomatic *C. difficile* carriage (positive follow-up cultures without any clinical symptoms) occurred in five (25%) vancomycin patients and two (7.7%) teicoplanin patients (\(P = 0.11\)). Overall, 9 of 20 (45%) vancomycin patients and 5 of 26 (19.2%) teicoplanin patients (\(P = 0.059\)) appeared not to be cured of *C. difficile* after treatment. No adverse effects related to vancomycin or teicoplanin therapy were observed.

Recent data indicate that *Clostridium difficile* is the most common agent of nosocomial diarrhea (32). Indeed, this microorganism is almost invariably involved in pseudomembranous colitis (PMC) and has been associated with at least one-fourth of all cases of diarrhea in hospitalized patients receiving antimicrobial therapy (20, 21, 26).

Nosocomial transmission of *C. difficile*, suggested by the clustering of cases (3, 7, 27), has been confirmed by using various epidemiological markers (5, 11-13, 34, 36); moreover, widespread contamination of the inanimate hospital environment (16, 29, 36), as well as carriage of the organism on the hands of hospital personnel (22, 25, 27, 28), has been extensively documented.

Mild cases of *C. difficile*-associated disease are often resolved by simply discontinuing the antibiotic responsible for infection, without the need for any specific therapy. On the other hand, in more severe cases, an antimicrobial agent effective against *C. difficile* should be given promptly (19).

*C. difficile* isolates are highly susceptible in vitro to many antibiotics, including vancomycin, metronidazole, bacitracin, rifampin (18), teicoplanin, amoxicillin-clavulanic acid, and the new (not commercially available) antimicrobial agents tiamcin B and C (35) and ramoplanin (3). Generally, vancomycin is considered the most suitable drug (14, 15, 24, 33, 37), with metronidazole and bacitracin considered useful alternatives (30). The clinical response to oral vancomycin treatment is usually very good and rapid (17), though relapse after treatment has been reported for 14 to 20% of patients (1, 17, 33) and posttreatment asymptomatic carriage of *C. difficile* has been found in as many as 28% of patients (17).

Teicoplanin, the newest glycopeptide antibiotic, is very active in vitro against *C. difficile* isolates (8, 30, 31). However, teicoplanin treatment of some cases of *C. difficile*-associated disease has been reported only by us (8, 9). In a previous study of 22 patients treated with oral teicoplanin (8), the clinical response and the rates of both posttreatment relapse and asymptomatic carriage were found to be very favorable and not statistically different from the corresponding data for historical controls (23 patients), who in the previous 3 years were treated with oral vancomycin. Thus, a prospective, randomized comparative study of teicoplanin and vancomycin was designed in order to define the role of teicoplanin in the treatment of *C. difficile*-associated disease.

(A preliminary report of this study has been presented previously [10].)

MATERIALS AND METHODS

Study population. From October 1989 to July 1991, all patients who developed diarrhea during their stay at the S. Bortolo Hospital (Vicenza, Italy) were investigated for the presence of both *C. difficile* and cytotoxin in their feces. Colonoscopy was also performed whenever possible. Relevant medical data for each patient, including the underlying disease, surgery, and the antimicrobial treatment received before the onset of symptoms, were recorded. Criteria for eligibility included an age of >18 years, absence of known sensitivity to glycopeptide antibiotics, presence of symptoms (diarrhea, sometimes combined with fever and abdom-
inal pain), and stool culture and/or a rapid diagnostic test positive for *C. difficile* and/or colonoscopic demonstration of the typical endoscopic picture of PMC.

**Diagnostic criteria.** Diarrhea was defined as the passing of more than three loose stools per day. *C. difficile*-associated diarrhea was diagnosed by demonstrating the presence of both *C. difficile* and cytotoxin in the feces of symptomatic patients in the absence of other intestinal pathogens and endoscopic evidence of colitis. The diagnosis of PMC was based also on the colonoscopic demonstration of typical endoscopic findings. The results of rapid diagnostic tests, such as latex agglutination assay (Cultrette brand CD latex test; Marion Scientific Inc., Kansas City, Mo.) and enzyme-linked immunoassays for the detection of toxin A (Premier [Meridian Diagnostics, Cincinnati, Ohio] and Vidas [Vitek Systems, Inc., Hazelwood, Mo.]) on stool suspensions, were considered only presumptive; they required confirmation by positive culture and toxin assay for all patients.

**Isolation and identification of *C. difficile*.** Stool samples were cultured anaerobically both by direct plating on CD Selective Blood Agar (Oxoid Ltd., Basingstoke, United Kingdom) supplemented with cefcloroxine (250 μg/ml) and cefoxitin (8 μg/ml) after heat shock (80°C for 10 min) and by culture in enrichment broth (4). The broth was subcultured on CD Selective Blood Agar after 24 h. The microorganism was identified by colony morphology, gas-liquid chromatography, and biochemical tests (23). Cytotoxin was identified by inoculating stool filtrates into 96-well microdilution plates seeded with Vero cells. Positive samples were confirmed by neutralization with specific antitoxin.

**Treatment regimen.** In order to choose the most suitable oral dosage of teicoplanin, preliminary assays of fecal teicoplanin concentrations in the samples from two patients affected with *C. difficile*-associated diarrhea (group A), not included in the prospective study, and nine normal volunteers (group B) were performed. Informed consent was obtained from all subjects. They were given different teicoplanin regimens. Group A patients were treated for 10 days with the dosage used in our previous study (8), i.e., 200 mg three times a day on day 1 and 200 mg twice a day thereafter. In contrast, group B volunteers were given only a single teicoplanin dose of either 50, 100, or 200 mg (three subjects each). The concentrations of teicoplanin in fecal samples of each bowel movement of each patient in group A and in samples of pooled daily feces of each group B volunteer were then determined. Prior to testing, one fourfold dilution of each stool sample in water (three parts) and bovine serum (one part), after homogenization with a Polytron apparatus (type PT 10-35; Kinematics AG), was stored at −80°C. Teicoplanin levels were assessed by using the receptor-antibody sandwich assay for teicoplanin (6). Teicoplanin concentrations in samples from group A patients were determined on each day of treatment (10 days), and in samples from group B volunteers, they were determined for a period of 5 days following the single-dose administration.

On the basis of the results obtained in this preliminary study (see below), we chose 100 mg twice a day as the dosage of teicoplanin for the prospective study.

For vancomycin, although most clinicians now give 125 mg four times a day, in this comparative study we chose to utilize the 2,000-mg/day regimen. Indeed, some authors (15) noted that diarrhea in very ill patients ceased slightly sooner with the higher dose of vancomycin. Eligible patients were thus randomized to receive, for 10 days, either oral vancomycin at 500 mg four times a day or oral teicoplanin at 100 mg twice a day. Patients were orally given vials for parenteral use because the oral formulation of neither drug was available in Italy. Informed consent was obtained from all subjects.

**Assessment of efficacy.** The efficacy of treatment was assessed by using both clinical and bacteriological criteria. The patients were considered clinically cured if they became asymptomatic (i.e., their symptoms and signs were eliminated). Clinical failure and clinical relapse were defined as persistence of diarrhea after 6 days of treatment and reappearance of diarrhea and other symptoms in the follow-up period, respectively. The clinical follow-up lasted at least 1 month. During this time, no patient received any antibiotic treatment. All patients were clinically checked and questioned about the number of bowel movements per day and stool consistence 7 to 10 days after discontinuation of the treatment and 25 to 30 days thereafter. On these occasions, stool samples were collected for *C. difficile* culture and cytotoxin assay. Moreover, the patients were instructed to contact one of the infectious-disease consultants if diarrhea or any other intestinal disturbance occurred later. From the microbiological point of view, cure was defined as the eradication of the infecting organism, and failure was defined as the persistence of *C. difficile* (with relapse) or without asymptomatic carriage clinical symptoms in one or both of the control cultures.

**Assessment of adverse reactions.** Adverse reactions were assessed by monitoring both clinical manifestations and laboratory parameters. Complete blood counts and renal and liver tests were performed 5 days after the beginning of therapy and at the end of the treatment.

**Statistics.** Results were analyzed with the two-tailed Fish-er's exact test on a personal computer by using the SAS statistical package (SAS Institute, Cary, N.C.).

**RESULTS**

**Preliminary study of subjects treated with different oral teicoplanin regimens.** The mean fecal concentrations of teicoplanin in group A patients, who received 200 mg three times a day on day 1 and 200 mg twice a day for 9 days thereafter, were 1,325 ± 525 μg/g (range, 946 to 2,413 μg/g), and they were maintained throughout the 10 days of treatment. For the volunteers given a single dose of teicoplanin (group B), fecal concentrations of this drug were detectable for at least 3 days, with mean peak concentrations (micrograms per gram) of 118 ± 17 (range, 106 to 137), 308 ± 161 (range, 158 to 478), and 708 ± 214 (range, 547 to 951) in patients given single 50-mg, 100-mg, and 200-mg doses of teicoplanin, respectively.

**Prospective study.** During our study, *C. difficile* cultures and cytotoxin assays were positive for 51 symptomatic patients hospitalized in different surgical and medical departments of S. Bortolo Hospital. Twenty-four patients were treated with vancomycin (500 mg four times a day for 10 days), and 27 patients received teicoplanin (100 mg twice a day for 10 days). Two patients died in the first days of treatment as a result of the underlying disease, and three patients dropped out of the study (two for protocol violation and one for coinfection with *Salmonella enteritidis*). Of the 46 assessable patients, 20 (6 males and 14 females) were given vancomycin and 26 (8 males and 18 females) received teicoplanin. The main features of the two treatment groups, as well as the response to therapy, are shown in Table 1. At the beginning of our study, all 46 assessable patients were receiving antibiotics or had been given an antimicrobial treatment in the previous week. Eighteen of the 20 patients...
in the vancomycin group and 10 of the 26 patients in the teicoplanin group had undergone surgery (P = 0.0004). A total of 19 patients (9 in the vancomycin group and 10 in the teicoplanin group) underwent colonoscopy, and typical endoscopic evidence of PMC was seen in 8 (88.9%) subjects in the vancomycin group and in 9 (90.0%) subjects in the teicoplanin group. Endoscopy was not performed on 11 patients receiving vancomycin or on 16 patients given teicoplanin. For all patients, treatment began during hospitalization, but three patients in the vancomycin group and nine patients in the teicoplanin group were discharged before treatment was completed. For these patients, therapy was continued at home. The remaining subjects, 17 in the vancomycin group and 17 in the teicoplanin group, were discharged from the hospital 25.6 ± 20.4 (range, 2 to 80) and 27.5 ± 18.3 (range, 2 to 64) days, respectively, after the treatment was completed.

As for the response to therapy, in the vancomycin group (Table 1), all patients appeared to be cured at the end of treatment. However, clinical symptoms recurred in four patients (20.0%) after discontinuation of therapy, and five asymptomatic subjects (25.0%) appeared to be colonized, as indicated by the follow-up cultures. Overall, seven (77.8%) of these nine C. difficile-positive patients were found not to be cleared of the microorganism by the time the first follow-up stool culture was done, and only two (22.2%) were found not to be cleared by the time the second follow-up stool culture was done. These nine patients were hospitalized in seven different departments of our hospital and in quite different periods during this study. All nine patients completed the course of treatment as inpatients, and for all but three of them, at least the first control samples were cultured during hospitalization. Indeed, the mean period of hospitalization after the end of treatment was 21.9 ± 11.7 (range, 19 to 38) days. Six of these patients were treated again with either vancomycin or teicoplanin (three patients each). All three subjects given teicoplanin (100 mg twice a day for 10 days) and two of the three who underwent a second course of vancomycin (same dosage as in the first course) appeared to be cleared of C. difficile 10 days after discontinuation of therapy.

In the teicoplanin group (Table 1), all but one patient appeared to be cured at the end of treatment. Clinical symptoms recurred in two patients (7.7%) after discontinuation of therapy. Furthermore, two more subjects (7.7%) were found to be asymptomatic carriers of C. difficile by control cultures. The only patient who showed an unsatisfactory clinical response to teicoplanin was a 57-year-old woman affected with a metastatic and inoperable colon cancer and Staphylococcus aureus sepsis. A few months before the study, she had also undergone a course of radiotherapy. Because of her poor clinical condition, colonoscopy could not be performed. After 5 days of oral teicoplanin treatment (concurrent with 600 mg of intravenous pefloxacin twice a day), fever abated, the number of daily bowel movements decreased from more than five to two or three, and stool consistency changed from watery to loose. However, at the end of treatment, this patient was having three bowel movements per day, with loose stool. The first control sample, cultured during hospitalization, was positive for C. difficile and negative for cytotoxin. The patient was discharged soon after the first control sample was cultured with no further follow-up. Overall, two of the five C. difficile-positive patients (40.0%) appeared not to be cleared of the microorganism by the time of the first control culture, and three (60.0%) appeared not to be cleared by the time of the second control culture. These five patients were hospitalized in five different departments; two of them were discharged before the end of the teicoplanin course, and they completed the treatment at home. The other three patients were hospitalized at least until the time of the first control culture (mean stay in the hospital after the end of treatment, 11.5 ± 2.1 days).

No adverse clinical events or significant changes in laboratory parameters, related to vancomycin or teicoplanin treatment, were observed.

**DISCUSSION**

The incidences of clinical relapse (20.0%) and asymptomatic carriage (25.0%) after vancomycin treatment in the present study are similar to those reported in the literature.

| TABLE 1. Treatment of C. difficile-associated disease with vancomycin and with teicoplanin* |
|-----------------|-----------------|-----------------|-----------------|
|                | Value for patients receiving: |                |                |
|                | Vancomycin        | Teicoplanin      |                |
| **No. of patients** |                |                |                |
| Tested         | 24              | 27              |                |
| Assessable (male/female) | 20 (6/14) | 26 (8/18) |                |
| With PMC (with colonoscopy*) | 8 (9) | 9 (10) |                |
| With previous antibiotic therapy (%) | 20 (100) | 26 (100) |                |
| With previous surgery (%) | 18 (90.0) | 10 (38.4) | 0.0004 |
| With treatment begun in hospital and continued after discharge (%) | 3 (12.0) | 9 (34.4) | 0.12 |
| **Time (days)** |                |                |                |
| To resolution of diarrhea | 3.6 ± 1.7 | 3.4 ± 1.4 | 0.62 |
| To defervesence | 2.7 ± 1.4 | 2.6 ± 1.6 | 0.76 |
| **No. of patients** |                |                |                |
| Clinically cured (%) | 20 (100) | 25 (96.2) | 0.56 |
| With clinical failure (%) | 0 | 1 (3.8) | 0.56 |
| With clinical relapse (%) | 4 (20.0) | 2 (7.7) | 0.21 |
| With asymptomatic carriage (%) | 5 (25.0) | 2 (7.7) | 0.11 |
| **Total no. of patients not cleared of C. difficile (%)** | 9 (45.0) | 5 (19.2) | 0.059 |

* Mean ages, 48 (range, 18 to 80) and 47 (range, 19 to 83) years for the vancomycin and teicoplanin groups, respectively.

* Fisher's exact test.

* Eleven patients in the vancomycin group and sixteen patients in the teicoplanin group did not undergo colonoscopy.
Indeed, posttreatment relapse and asymptomatic carriage have been found in 14 to 20% and as many as 28%, respectively, of patients treated with vancomycin (1, 17, 33). It should also be noted that 13 of the 20 assessable patients (and 6 of the 9 found not to be cleared of *C. difficile* after therapy) were discharged from the hospital only after the first control sample was cultured (range of posttreatment hospital stay, 10 to 80 days). It is, therefore, possible that some cases categorized as relapses may actually represent exogenous reinfection acquired in the hospital setting. Moreover, all but two patients had undergone surgery, which is a well-known risk factor for both *C. difficile*-associated disease and carrier status.

The results we obtained with teicoplanin-treated patients must be considered very good. Indeed, the overall incidence of microbiological failure (19.2%) is among the lowest reported in the literature on the efficacies of the antibiotic regimens used to treat *C. difficile*-associated disease. An even more favorable result (4.5% posttreatment carriage, without any clinical relapse) was obtained in our previous study (performed in another general hospital) on the value of teicoplanin for treatment of *C. difficile*-associated disease (8). That result could certainly be due to the higher doses of teicoplanin (200 mg twice a day) given in the previous study. However, some differences in hospital environment and in the study populations of these two studies (such as the longer period of hospitalization after treatment in the present study) are probably much more important. Indeed, among the subjects who received the same vancomycin regimen (500 mg four times a day for 10 days), 17.3% of the patients in the previous study (8) and 45.0% of the patients in the present study were not cleared of the microorganism after therapy.

One patient given teicoplanin improved, but the overall response to treatment was considered unsatisfactory. However, the fact that this subject was affected with metastatic colonic cancer and had previously undergone a course of radiotherapy should be taken into account. Thus, the clinical and microbiological failures could possibly be due to failure of the drug to reach the infected areas of the bowel. In addition, an unsuccessful response to specific therapy has occasionally been reported by others (19).

The preliminary study on fecal concentrations of orally given teicoplanin shows that in cases of *C. difficile*-associated disease, after administration of 200 mg every 8 h on day 1 and twice a day for 9 days thereafter, mean fecal levels of this drug are very high, ranging from 946 to 2,413 μg/g. Most *C. difficile* strains are susceptible to 0.250 μg of teicoplanin per ml (8). Considering also the cost of this drug, we chose 100 mg twice a day as the dosage of teicoplanin in the prospective study comparing this drug with oral vancomycin. Indeed, after a single oral dose of 100 mg, peak fecal levels of teicoplanin in healthy volunteers ranged from 158 to 478 μg/g. It is possible, however, that in diarrheic patients with watery stools and accelerated intestinal transit, higher or more frequent doses would be more effective.

In conclusion, this prospective, randomized comparative study confirms the efficacy and the safety of oral teicoplanin in the treatment of PMC and *C. difficile*-associated diarrhea. The twice-daily administration of 100 mg of this drug for 10 days seems to be as effective as the four-times-daily administration of 500 mg of vancomycin for 10 days. However, the most effective number of doses of teicoplanin per day, as well as the most suitable amount of drug per dose, remains to be determined.

**ACKNOWLEDGMENT**

We are grateful to L. Cavenagh (Lepetit Research Center, Gerenzano, Italy) for assessing the fecal concentrations of teicoplanin.

**REFERENCES**


