ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1996, p. 696–700 Vol. 40, No. 3
0066-4804/96/$04.00+0
Copyright © 1996, American Society for Microbiology

Comparison of Conventional Dosing versus Continuous-Infusion Vancomycin Therapy for Patients with Suspected or Documented Gram-Positive Infections

JOSEPH K. JAMES,[1]† SHIRLEY M. PALMER,[1]‡ DONALD P. LEVINE,[2] AND MICHAEL J. RYBAK[1,2]*

The Anti-Infective Research Laboratory, Department of Pharmacy Services, Detroit Receiving Hospital and University Health Center and College of Pharmacy and Allied Health Professions,[1] and Division of Infectious Diseases, Department of Internal Medicine, School of Medicine,[2] Wayne State University, Detroit, Michigan 48201

Received 3 July 1995/Returned for modification 27 October 1995/Accepted 22 December 1995

Ten patients were treated with conventional dosing (CD) and continuous-infusion (CI) vancomycin therapy in this prospective, randomized, crossover study. Patients were randomized to receive either CD or CI therapy for 2 consecutive days and then crossed over to receive the opposite regimen for 2 days. CD therapy consisted of 1 g of vancomycin every 12 h. CI therapy consisted of a 500-mg loading dose followed by 2 g infused over 24 h. Ten serum samples were obtained on the second day of each therapy for pharmacokinetic and pharmacodynamic analyses. Two clinical isolates of *Staphylococcus aureus*, one methicillin sensitive (MSSA 1199) and one methicillin resistant (MRSA 494), were chosen for pharmacodynamic evaluation of both regimens. The patient demographics (means ± standard deviations [SD]) were as follows: sex, six males, four females; age, 36 ± 11 years; and serum creatinine, 0.72 ± 0.18 mg/dl. Mean pharmacokinetic parameters ± SD for CD therapy were as follows: elimination rate constant, 0.16 ± 0.07 h^{-1}; half-life, 5.6 ± 3.5 h; volume of distribution, 33.7 ± 25 liters, 0.5 ± 0.2 liters/kg; maximum concentration in serum, 53.4 ± 19.3 μg/ml; and minimum concentration, 8.4 ± 5.9 μg/ml. The steady-state concentration for CI was 20.2 ± 11.1 μg/ml. Overall, both regimens resulted in the MIC being exceeded 100% of the time. The mean CD trough serum bactericidal titer (SBT) was 1:8, and the average CI SBTs were 1:16 for both isolates. Even though there was no statistically significant difference between CD trough and CI SBTs, the CI SBTs remained >1:8 for 100% of the time versus 60% of the time for CD therapy. During CI therapy, 20 and 40% of the patients maintained SBTs of >1:32 throughout the dosing interval for MSSA 1199 and MRSA 494, respectively. During CD therapy, however, only 10% of patients maintained SBTs of >1:32 during the entire dosing interval for both isolates. The mean areas under the bactericidal titer-time curve ($AUBC_{24}$s) ± SD for MSSA 1199 were 528 ± 263 for CD therapy and 547 ± 390 for CI therapy. The mean $AUBC_{24}$s ± SD against MRSA 494 were 531 ± 247 for CD and 548 ± 293 for CI therapy. Similar to the $AUBC_{24}$, the mean area under the concentration-time curve for a 24-h dosing interval divided by the MIC (AUC/MIC_{24}) ratios ± SD were 550.0 ± 265.7 for CD and 552.6 ± 373.4 for CI therapy, respectively. No statistically significant differences were found between any of the pharmacodynamic parameters for CD and CI therapy. In addition, no adverse effects with either CD or CI therapy were observed during the study. We conclude that CI and CD vancomycin therapy demonstrated equivalent pharmacodynamic activities. Although CI therapy was more likely to result in SBTs that remained above 1:8 for the entire regimen, the clinical impact of this result is unknown. Serum drug concentration variability was observed with both treatment regimens but to a lesser extent with CI administration. CI administration of vancomycin should be further evaluated to determine the clinical utility of this method of administration.

The use of vancomycin continues to increase as resistant gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) strains, *Staphylococcus epidermidis*, and ampicillin-resistant *Enterococcus* isolates, become more prevalent (23, 32). In terms of clinical outcome, however, little regarding the relationship of serum vancomycin concentrations and response is known. The current practice of obtaining specific peak and trough serum drug concentrations is not based upon sound pharmacodynamic principles. Rather, these methods appear to be founded on the notion of obtaining concentrations at some multiple of the MIC while avoiding toxicities which have been reported to occur with specific peak and/or trough serum drug concentrations (11, 35). Aminoglycosides are currently dosed on the premise that high peak concentrations are critical for bacterial killing and that elevated trough concentrations are responsible for drug-related toxicities (16, 18, 19, 22). There is little evidence, however, that supports the application of these principles to vancomycin dosing. In contrast to aminoglycosides, vancomycin does not exhibit concentration-dependent killing. Beta-lactam and glycopeptide antibiotics are bactericidal independent of their concentrations in serum and are believed to achieve maximum killing at concentrations in serum of four to five times the MIC for the infecting organism (1, 29, 30). It has been suggested that vancomycin should be administered to maximize the time that antimicrobial agent concentrations exceed the MIC (T>MIC) for the suspected pathogen (9, 15). This may require shorter dosing

* Corresponding author. Mailing address: The Anti-Infective Research Laboratory, Department of Pharmacy Services, Detroit Receiving Hospital, 4201 St. Antoine Blvd., Detroit, MI 48201. Phone: (313) 745-4554. Fax: (313) 993-2522.

† Present address: Department of Pharmacy, Boston City Hospital, Boston, MA 02115.

‡ Present address: Department of Pharmacy Practice, College of Pharmacy, University of Florida, Gainesville, FL 32610-0486.

intervals or continuous infusions (CIs) to prevent bacterial regrowth and ensure drug efficacy. Data for the administration of vancomycin by CI are extremely limited (2, 4, 34).

Pharmacodynamic parameters have been employed to describe different rates of bacterial eradication in relation to varying concentrations in serum for drugs exhibiting concentration-independent killing activity. These parameters include trough serum bactericidal titers (SBTs), area under the bactericidal titer-time curve for 24 h ($AUBC_{24}$), the area under the concentration-time curve for a 24-h dosing interval divided by the MIC (AUC/MIC_{24}), and T>MIC. The SBT reflects the interaction of a patient's serum containing an antimicrobial agent and the in vitro susceptibility of the organism. The determination of the SBT may allow direct comparisons between drugs or dosing regimens by the integration of patient characteristics, such as pharmacokinetics and immune factors, and in vitro activity. An SBT of 1:8 has been associated with successful treatment of staphylococcal infections with vancomycin (15, 29). An inability to achieve adequate SBTs may indicate the need for an alternative antimicrobial agent or a change in the dose or dosing schedule. The $AUBC_{24}$ is calculated from serial measurements of the SBT, and it has been proposed to be a rational method for comparison of antimicrobial agents (3). T>MIC, usually measured in hours, appears to be the most appropriate parameter for measuring the efficacy of concentration-independent antimicrobial agents. On the basis of the pharmacodynamic characteristics of vancomycin, this parameter should be the most important for predicting efficacy. The objective of this trial was to determine and compare the pharmacodynamic parameters of conventional dosing (CD) and CI vancomycin therapy in patients with suspected or documented gram-positive infections.

MATERIALS AND METHODS

Patients. All patients who were admitted to Detroit Receiving Hospital and University Health Center and who were prescribed vancomycin by their physician for presumed or documented gram-positive infections were eligible for enrollment in the study. Patients receiving either cephalosporins or aminoglycosides in addition to vancomycin for empiric therapy were also included, as these agents could be inactivated or removed from serum samples prior to pharmacodynamic analysis. This study was approved by the Human Investigations Review Board at our institution. Informed consent was obtained from all patients who were >18 years old or from their guardians for patients <18 years old prior to participation in the study. Exclusion criteria consisted of a history of hypersensitivity to vancomycin, a life expectancy of <48 h, renal dysfunction (serum creatinine of >2.5 mg/dl or estimated creatinine clearance of <40 ml/min), age of <17 years, or an inability to obtain informed consent. Initial patient demographic data, including age, sex, weight, height, and infectious diagnosis, were collected upon enrollment in the study. Serum creatinine was measured and creatinine clearance was estimated on each day of the study (8).

Study design. This study was a prospective, randomized, crossover study to compare the pharmacodynamics of CD and CI vancomycin therapy in patients with suspected or documented gram-positive infections. The patients were prescribed vancomycin by their physicians for the treatment of gram-positive infections and were enrolled in this study within 48 h of initiation of vancomycin therapy. The patients were then randomized to receive either CD or CI vancomycin therapy for 2 consecutive days and then crossed over to receive the opposite regimen for 2 days. Steady-state vancomycin concentrations were expected to be achieved on the second day of each treatment regimen for pharmacokinetic and pharmacodynamic analyses. The patients were returned to CD vancomycin therapy after the completion of the 4-day study period.

Antimicrobial agent administration. All patients enrolled in the study received vancomycin (Vancocin; Eli Lilly and Company, Indianapolis, Ind.), which was reconstituted according to the manufacturer's guidelines. CI vancomycin therapy consisted of a 500-mg loading dose diluted in 100 ml of 5% dextrose in water and administered over 30 min (24). Following the loading dose, 2,000 mg of vancomycin diluted in 250 ml of 5% dextrose in water was infused over 24 h by a constant infusion pump set at 11 ml/h (6000+ Programmable Infusion Pump; Sigma, Medina, N.Y.). At this rate, it was estimated that approximately 80 mg of vancomycin was delivered per h, which was expected to achieve an average concentration of 15 μg/ml (14). For CD vancomycin therapy, 1,000 mg was diluted in 250 ml of 5% dextrose in water and administered over 60 min every 12 h. This dose was expected to provide peak and trough concentrations of 25 to 35 and 5 to 10 μg/ml, respectively (27, 28).

Blood samples. Serial blood samples (approximately 3 ml) were collected from a central-line catheter or a heparin lock which was placed in the forearm opposite the infusion site for pharmacokinetic and pharmacodynamic analyses. Samples were obtained on the first day of CI vancomycin therapy just prior to the administration of the loading dose, at the end of the loading dose for pharmacokinetic analysis, and on day 2 at 24, 36, and 48 h for pharmacodynamic evaluation following the initiation of the CI. For standard-dosing vancomycin therapy, samples were obtained on the second day before the 1-h infusion, at the end of the 1-h infusion, and 2, 8, and 12 h after the beginning of the infusion. Specimens for serum drug concentration determinations and pharmacodynamic analysis were collected in red-top tubes, allowed to clot for approximately 45 min, centrifuged for 10 min at 4,500 × *g*, split into two aliquots, and transferred to sterile polypropylene tubes. One aliquot was used to determine vancomycin concentrations, and the other was used to perform pharmacodynamic analysis. Samples for vancomycin concentrations were frozen at −20°C until analysis.

Analytical method. Concentrations of vancomycin in serum were determined by fluorescence polarization immunoassay (TDx; Diagnostic Division, Abbott Laboratories, Irving, Tex.). The assay limits and intraday and between-day coefficients of variation for vancomycin were 0.6 μg/ml and <6%, respectively (27). The linearity (r^2) of the assay was 0.999.

Test organisms and susceptibilities. Two clinical isolates of *S. aureus*, one methicillin-sensitive strain (MSSA 1199) and one methicillin-resistant strain (MRSA 494), were used for SBT determinations. MICs and MBCs for the two clinical isolates were determined in quadruplicate by the microdilution method according to guidelines from the National Committee for Clinical Laboratory Standards (NCCLS) using vancomycin hydrochloride analytical powder (lot 112HO75025; Sigma Chemical Co., St. Louis, Mo.) (21).

Pharmacokinetic analysis. Data for vancomycin concentrations in serum versus time were fit to polyexponential functions with a nonlinear least-squares regression program (12). The minimum number of exponentials needed to describe the curve was determined with a modified Akaike Information Criteria test with a weighting factor of $1/y^2$ (12). The AUC over the dosing interval was calculated by the linear trapezoidal rule with the LAGRAN program (26). The steady-state volume of distribution was calculated by using the formula of Gibaldi and Perrier (14). The area under the first nonnormalized moment curve after single-dose administration from zero to infinity was estimated by the method of Smith and Schentag, which provides a means for calculating this parameter from steady-state data (31).

Pharmacodynamic analysis. SBTs were determined in duplicate for each serum sample for MSSA 1199 and MRSA 494 according to the proposed NCCLS guidelines (20). Aminoglycosides (gentamicin and tobramycin) were removed from the samples by the addition of 15 mg of cellulose phosphate (lot 125F0252; Sigma Chemical Co.) to approximately 0.5 ml of serum. The samples were allowed to sit for 15 min and then were centrifuged at 4,500 × *g* for 10 min. Serum samples were assayed before and after the addition of cellulose phosphate to verify the stability of vancomycin and the removal of the aminoglycosides. Expanded-spectrum cephalosporins (ceftazidime and ceftizoxime) were inactivated by the addition of 25 μl of purified Bush class 1 β-lactamase to 0.5 ml of serum (6). The β-lactamase (Q908R) was obtained from an *Enterobacter cloacae* isolate and differs in only four amino acids from the closely related P99 enzyme (5). After the addition of β-lactamase, the samples were allowed to sit for 15 min and vortexed. Verification of the inactivation of the cephalosporins was done by determining the MICs for *Enterobacter aerogenes* 3893 before and after addition of the enzyme. MIC determinations were made with serum spiked with ceftazidime (400 μg/ml) (lot Z90043EY; Glaxo Pharmaceuticals, Research Triangle Park, N.C.) and ceftizoxime (400 μg/ml) (lot 525C17; Fujisawa, Deerfield, Ill.). The MICs of ceftazidime and ceftizoxime for *E. aerogenes* were <0.5 and 1.25 μg/ml, respectively; these values increased to >50 μg/ml for both antibiotics after the addition of the β-lactamase.

An SBT of ≥1:8 was considered adequate for trough SBTs for CD therapy and for mean SBT values for CI vancomycin therapy (20). The ability to obtain an SBT of ≥1:32 was also evaluated, since this value has been suggested as adequate for bacterial endocarditis (33, 36).

The AUBC was calculated with the trapezoidal rule by plotting the reciprocal of the SBT as a function of time for each regimen and clinical isolate (3, 26). For the CI therapy, the AUBC was calculated for a 24-h dosing interval (0 to 24 or 24 to 48 h). The CD therapy AUBC was determined for a 12-h dosing interval (24 to 36 or 36 to 48 h). This value was then multiplied by two to determine the $AUBC_{24}$ for the purpose of comparisons between the two regimens. The AUC/MIC_{24} was also calculated for each of the test strains (30) by using the trapezoidal rule (26).

T>MIC for each isolate was determined from visual inspection with interpolation of the serum vancomycin concentration-versus-time plot for both dosing regimens.

Statistical analysis. Fisher's exact test was used to determine whether CD and CI vancomycin therapy against each clinical isolate achieved adequate SBT parameters (percentages of patients with SBTs of ≥1:8 and ≥1:32 for the entire dosing interval). A paired Student's *t* test was used to determine differences in pharmacodynamic parameters (trough SBT, $AUBC_{24}$, AUC/MIC_{24}, and T>MIC) between the two treatment groups and to compare trough vancomycin

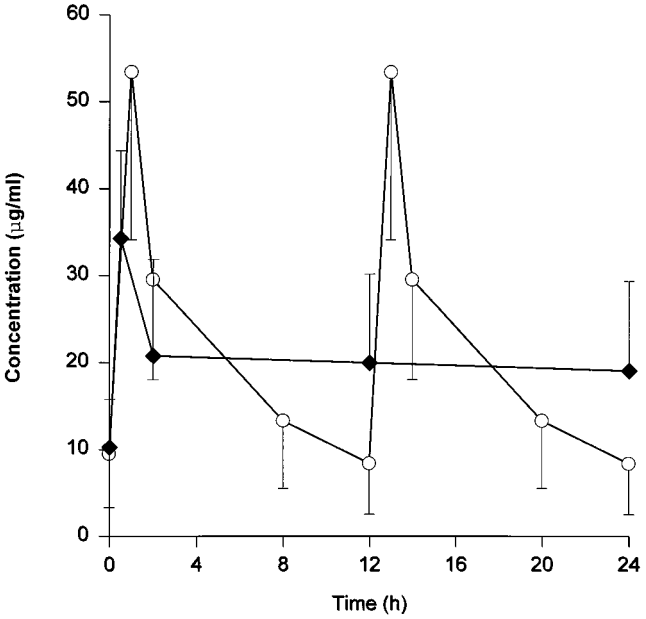

FIG. 1. Mean serum vancomycin concentrations adapted to a 24-h dosing interval. ○, CD; ◆, CI. The results for the concentration-time dosage interval of 12 to 24 h was simulated from mean data for 0 to 12 h.

concentrations to verify attainment of steady state. A P value of <0.05 was considered significant.

RESULTS

Susceptibility testing. The MICs were 0.78 μg/ml and the MBCs were 1.56 μg/ml for both isolates.

Patient demographics. Ten patients (six men and four women), five of whom were intensive care unit patients, were enrolled in the study. Three patients (two men and one woman) were active intravenous drug abusers. Five patients received other antibiotics, including gentamicin, tobramycin, ceftazidime, and ceftizoxime, which were eliminated or inactivated from the serum before pharmacodynamic analysis. The mean age ± standard deviation (SD) was 36 ± 11 years, and the mean weight ± SD was 86 ± 38 kg. The mean serum creatinine and estimated creatinine clearance ± SD were 0.72 ± 0.18 mg/dl and 110 ± 30 ml/min, respectively. Infectious diagnosis included bacteremia (n = 2), line site infections (n = 2), a urinary tract infection (n = 1), osteomyelitis (n = 2), cellulitis (n = 1), pneumonia (n = 1), and a brain abscess (n = 1).

Pharmacokinetic parameters. Serum vancomycin concentrations (means ± SD) for both regimens adapted to a 24-h dosing interval are shown in Fig. 1. Pharmacokinetic parameters (means ± SD) for CD therapy were as follows: elimination rate constant, 0.16 ± 0.07 h^{-1}; elimination half-life, 5.6 ± 3.5 h; volume of distribution, 33.7 ± 25 liters, 0.5 ± 0.2 liters/kg; maximum concentration in serum (C_{max}), 53.4 ± 19.3 μg/ml; and minimum concentrations (C_{min}s), 8.4 ± 5.9 and 9.5 ± 6.2 μg/ml for 24 versus 36 h, respectively. No statistically significant differences were detected between trough concentrations ($C_{min2} - C_{min1}$, 1.2 ± 0.3 μg/ml) in samples drawn on the second day of therapy, indicating that vancomycin was at steady state. Pharmacokinetic parameters (means ± SD) for CI therapy were as follows: C_{max} following the loading dose, 35.3 ± 9.5 μg/ml; C_{min} prior to the loading dose in patients randomized to CI after CD therapy, 10.3 ± 5.5 μg/ml; and steady-state concentration, 20.2 ± 11.1 μg/ml.

Pharmacodynamic parameters. Pharmacodynamic parameters are summarized in Table 1. Both regimens resulted in a T>MIC of 100% for both isolates. The mean CD trough and mean CI SBTs for both isolates were 1:8 and 1:16, respectively. The percentages of patients whose SBTs remained above 1:8 during the entire dosing interval were 60% for CD and 100% for CI therapy for both isolates. Ten percent of the patients receiving CD therapy maintained SBTs above 1:32 during the entire dosing interval for both isolates. The percentages of patients whose SBTs remained above 1:32 throughout the CI were 20% for MSSA 1199 and 40% for MRSA 494. The $AUBC_{24}$s (means ± SD) for MSSA 1199 were 528 ± 263 for CD and 547 ± 390 for CI therapy. The $AUBC_{24}$s (means ± SD) for MRSA 494 were 531 ± 247 for CD and 548 ± 293 for CI therapy. Similar to the $AUBC_{24}$, the mean AUC/MIC_{24}s were 550.0 ± 265.7 for CD and 552.6 ± 373.4 for CI therapy, respectively. No statistically significant differences between any of the pharmacodynamic parameters for CD and CI therapy against either isolate were detected.

Safety and tolerance of study drug. No adverse effects, including infusion-related adverse effects, were observed during the study with the CD or CI therapy. Furthermore, no changes in serum creatinine or creatinine clearance occurred during the 4-day study period. Mean serum creatinine and creatinine clearance values ± SD on days 1 and 4 were 0.70 ± 0.19 mg/dl and 110 ± 30 ml/min and 0.71 ± 0.17 mg/dl and 107 ± 32 ml/min, respectively.

DISCUSSION

The use of vancomycin has increased dramatically over the last decade because of the appearance of resistant gram-positive organisms. With this increased use, controversies regarding the most appropriate way to administer and monitor vancomycin have developed (7, 10, 13, 17, 25, 37). Vancomycin is currently administered by intermittent infusion to produce specific peak and trough concentrations for efficacy and to avoid potential serum drug concentration-related side effects, such as ototoxicity or nephrotoxicity, on the basis of toxicity principles similar to those for aminoglycosides. In contrast to aminoglycosides, however, vancomycin demonstrates concentration-independent killing which is maximized at concentrations of four or five times the MIC for the organism (1, 29, 30). Administering vancomycin as a CI and maintaining a constant concentration in serum of four or five times the MIC for the infecting organism may be the ideal way to deliver this antibiotic for serious infections. In addition, as opposed to the case for aminoglycosides, there is no conclusive evidence that there exists a relationship between concentrations in serum and oto-

TABLE 1. Pharmacodynamic parameters of CD and CI vancomycin therapy against MSSA 1199 and MRSA 494[a]

Schedule	Isolate	SBT[b]	AUC/MIC_{24}	$AUBC_{24}$	% SBT[c]	
					≥1:8	≥1:32
CD	MSSA	1:8	550.0 ± 265.7	528.4 ± 263.7	60	10
	MRSA	1:8	550.0 ± 265.7	531.4 ± 247.1	60	10
CI	MSSA	1:16	552.6 ± 373.4	547.5 ± 390.7	100	20
	MRSA	1:16	552.6 ± 373.4	548.4 ± 293.4	100	40

[a] For both isolates and both therapies, T>MIC was 100% for the 24-h dosing interval.
[b] Mean trough SBT for CD vancomycin and mean SBT for CI therapy.
[c] Percentage of patients whose SBTs remained above the indicated value for the entire dosing interval.

toxicity or nephrotoxicity (7, 17, 25). Therefore, until proven otherwise, it seems unwarranted to monitor specific serum drug concentrations for the purpose of avoiding toxicity.

To our knowledge, no reports of prospective clinical trials examining the pharmacodynamics of CI vancomycin therapy have been published. Three case series and one abstract have been published, with minimum information regarding the pharmacokinetics and pharmacodynamics of vancomycin administered as a CI. Thomas and colleagues (34) described three adults with staphylococcal septicemia treated with CIs of vancomycin. The dose of vancomycin ranged from 500 mg/day to 3 g/day, which produced a range of concentrations in serum from 7 to 34 μg/ml (mean, 18 μg/ml). All patients were reported to have been cured (34). Barois and colleagues (2) reported 13 cases of staphylococcal central nervous system infections and one case of septicemia in children treated with CIs of vancomycin. The patients received 40 mg/kg/day, which achieved a mean serum vancomycin concentration of 18 μg/ml. No treatment failures were reported (2). Brinquin and colleagues (4) discussed the use of continuous vancomycin infusion in eight adult patients with postsurgery meningitis caused by MRSA. Mean vancomycin doses of 50 mg/kg of body weight per day were used, and the duration of therapy ranged from 3 to 6 weeks. Serum vancomycin concentrations ranged from 19 to 46 μg/ml. The therapy was well tolerated and was reported to have resulted in cure in all cases (4).

We conducted this prospective, randomized, crossover study to determine and compare the pharmacodynamics of CD and CI vancomycin therapy in patients with suspected or documented gram-positive infections. T>MIC seems to be the most important parameter for the efficacy of vancomycin because of its concentration-independent killing activity. For both CD and CI therapy, the vancomycin concentration remained above the MIC throughout the dosing period. Despite the fact that this was a crossover study designed to reduce variability between the two dosage regimens, there was considerable variability in the serum vancomycin concentrations. The C_{max} and C_{min} for CD therapy ranged from 31.44 to 87.93 and 2.5 to 22.4 μg/ml, respectively. The C_{max} and C_{min} (trough concentration prior to CI initiation) for the CI therapy ranged from 26.5 to 43.1 and 3.9 to 19.3 μg/ml, respectively. The steady-state concentration for CI therapy ranged from 7.96 to 43.0 μg/ml. Reasons for some of the variability in vancomycin concentrations, which include differences in severity of illness and renal clearance and whether or not patients were intravenous drugs users, have been reported previously (27).

It is not known what vancomycin concentration would be the most efficacious for the treatment of serious staphylococcal infections. The target concentration that we chose for this trial of CI vancomycin therapy was 15 μg/ml. This was based on a conservative approach to obtain a concentration well above four or five times the typical MIC for *S. aureus*. A dose of 2 g over 24 h produced a steady-state concentration (mean ± SD) of 20.2 ± 11.11 μg/ml, with a range from 7.96 to 43.0 μg/ml. These results indicate that in some patients, the steady-state serum vancomycin concentrations were well below the 15-μg/ml target concentration. Because of this degree of variability, an initial target concentration of 20 μg/ml may be more appropriate for the treatment of serious gram-positive infections. Despite the variability in CI vancomycin concentrations in serum, the SBTs remained ≥1:8 throughout the CI.

The mean trough SBT for CD therapy was 1:8 for both isolates of *S. aureus*. The mean SBT for CI therapy was 1:16. No statistically significant difference was detected between trough and mean CI SBTs, and both SBTs are considered adequate according to the NCCLS guidelines.

Although the percentages of patients whose SBTs remained above 1:8 and 1:32 were not significantly different, there was a trend toward more patients receiving CI therapy maintaining these values for the entire dosing interval than patients receiving the CD therapy. All 10 patients maintained SBTs above 1:8 while receiving CI vancomycin therapy. In addition, CI therapy was more likely to maintain SBTs as high as 1:32, in contrast to CD therapy.

The $AUBC_{24}$ has been advocated as a potential method for evaluating antibiotic efficacy (3). However, the relationship between the size of the $AUBC_{24}$ and antibiotic efficacy as well as the utility of this method for prediction of outcome has not been evaluated clinically. Studies specifically addressing whether $AUBC_{24}$s or SBTs are reliable means of predicting efficacy should be conducted to help clarify these issues. We also evaluated the AUC/MIC_{24}. The fact that the $AUBC_{24}$ and the AUC/MIC_{24} were similar implies that the contribution of the patient's serum was minimal. However, this may be a function of the way in which the serum titers are derived, since the contribution of the patient's serum could be minimized by the diluting medium. Although there have been several studies examining the relationship between AUC/MIC and efficacy for several different antibiotic classes, glycopeptides such as vancomycin have not been evaluated. On the basis of vancomycin's concentration-independent properties, use of trough concentrations and T>MIC seems to be the most logical approach to evaluating this antimicrobial agent. Despite the variability between serum vancomycin concentrations, however, we found no statistically significant differences in $AUBC_{24}$, AUC/MIC_{24}, or T>MIC between the two dosing regimens. On the basis of its relatively long elimination half-life, vancomycin administered in equivalent doses at shorter dosing intervals, such as every 6 or 8 h, should provide less variability and produce concentrations in serum similar to that achieved with the CI regimen.

We conclude that CD and CI vancomycin therapy demonstrated equivalent pharmacodynamic activities against MSSA 1199 and MRSA 494. Although CI therapy was more likely to result in SBTs that remained above 1:8 for the entire dosing interval, it is unknown whether this would result in improved patient outcome. Our study results should be noted with caution, since this investigation utilized a relatively small patient population and did not attempt to evaluate efficacy. The value of CI therapy should be further examined to determine the clinical efficacy of this method of administration of vancomycin.

ACKNOWLEDGMENTS

We thank A. Bulychev, Department of Chemistry, Wayne State University, for kindly providing the β-lactamase. We also thank Abbott Laboratories for the use of the fluorescence polarization immunoassay analyzer for the determination of vancomycin concentrations.

REFERENCES

1. **Ackerman, B. H., A. M. Vanniere, and E. B. Eudy.** 1992. Analysis of vancomycin time-kill studies with *Staphylococcus* species by using a curve stripping program to describe the relationship between concentration and pharmacodynamic response. Antimicrob. Agents Chemother. **36:**1766–1769.
2. **Barois, A., B. Estournet, J. B. Moranne, J. Piliot, C. Chabenat, and J. Bataille.** 1986. Staphylococcal infection of cerebral ventricles treated with vancomycin by continuous infusion. Presse Med. **15:**1805–1808.
3. **Barriere, S. L., E. Ely, J. E. Kapusnik, and J. G. Gambertoglio.** 1985. Analysis of a new method for assessing activity of combinations of antimicrobials: area under the bactericidal activity curve. J. Antimicrob. Chemother. **16:**49–59.
4. **Brinquin, L., J. M. Rousseau, G. Boulesteix, Y. Diraison, and J. P. Bonsignour.** 1993. Continuous infusion of vancomycin in post-neurosurgical staphylococcal meningitis in adults. Presse Med. **22:**1815–1817.
5. **Bulychev, A. (Wayne State University).** 1995. Personal communication.

6. **Bush, K.** 1989. Classification of β-lactamases: groups 1, 2a, 2b, and 2b. Antimicrob. Agents Chemother. **33:**264–270.
7. **Cantu, T. G., N. A. Yamanaka-Yuen, and P. S. Lietman.** 1994. Serum vancomycin concentrations: reappraisal of their clinical value. Clin. Infect. Dis. **18:**533–543.
8. **Cockroft, D. W., and M. H. Gault.** 1976. Prediction of creatinine clearance from serum creatinine. Nephron **16:**31–41.
9. **Craig, W. A., and S. C. Ebert.** 1992. Continuous infusion of β-lactam antibiotics. Antimicrob. Agents Chemother. **36:**2577–2583.
10. **Edwards, D. J., and S. Pancorbo.** 1987. Routine monitoring of serum vancomycin concentrations: waiting for proof of its value. Clin. Pharm. **6:**652–654.
11. **Farber, B. F., and R. C. Moellering.** 1983. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. Antimicrob. Agents Chemother. **23:**138–141.
12. **Fox, J. L., and M. L. Lamson.** 1987. RSTRIP user handbook. MicroMath, Inc., Salt Lake City, Utah.
13. **Freeman, C. D., R. Quintiliani, and C. H. Nightingale.** 1993. Vancomycin therapeutic drug monitoring: is it necessary? DICP Ann. Pharmacother. **27:**594–598.
14. **Gibaldi, M., and J. D. Perrier.** 1982. Pharmacokinetics, 2nd ed., p. 414. Marcel Dekker, Inc., New York.
15. **Louria, D. B., T. Kaminski, and J. Buchman.** 1961. Vancomycin in severe staphylococcal infections. Arch. Intern. Med. **107:**225–240.
16. **Mattie, H., W. A. Craig, and J. C. Pechere.** 1989. Review: determinants of efficacy and toxicity of aminoglycosides. J. Antimicrob. Chemother. **24:**281–293.
17. **Moellering, R. C., Jr.** 1994. Editorial: monitoring serum vancomycin levels: climbing the mountain because it is there? Clin. Infect. Dis. **18:**544–546.
18. **Moore, R. D., P. S. Lietman, and C. R. Smith.** 1984. The association of aminoglycoside plasma levels with mortality in patients with gram-negative pneumonia. J. Infect. Dis. **149:**443–448.
19. **Moore, R. D., P. S. Lietman, and C. R. Smith.** 1987. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J. Infect. Dis. **155:**93–97.
20. **National Committee for Clinical Laboratory Standards.** 1992. Methodology for the serum bactericidal test. Tentative guidelines. Document M21-T. National Committee for Clinical Laboratory Standards, Villanova, Pa.
21. **National Committee for Clinical Laboratory Standards.** 1993. Methods for dilution and antimicrobial susceptibility tests for bacteria that grow aerobically, 3rd ed. Approved standard. Document M7-A3. National Committee for Clinical Laboratory Standards, Villanova, Pa.
22. **Noone, P., T. M. C. Parsons, J. R. Pattison, R. C. B. Slack, D. Garfield-Davies, and K. Hughes.** 1974. Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. Br. Med. J. **i:**477–481.
23. **Oster, S. E., V. A. Chirurgi, A. A. Goldberg, S. Aiken, and R. E. McCabe.** 1990. Ampicillin-resistant enterococcal species in an acute-care hospital. Antimicrob. Agents Chemother. **34:**1821–1823.
24. **Polk, R. E., D. P. Healy, L. B. Schwartz, D. T. Rock, M. L. Garson, and K. Roller.** 1988. Vancomycin and the red-man syndrome: pharmacodynamics of histamine release. J. Infect. Dis. **157:**502–507.
25. **Pryka, R. D.** 1994. Vancomycin serum concentration monitoring: a continued debate. DICP Ann. Pharmacother. **28:**1397–1399.
26. **Rocci, M. L., Jr., and W. J. Jusko.** 1983. LAGRAN program version 2.1 for area and moments in pharmacokinetic analysis. Comput. Programs Biomed. **16:**203–216.
27. **Rybak, M. J., L. M. Albrecht, J. R. Berman, L. H. Warbasse, and C. K. Svensson.** 1990. Vancomycin pharmacokinetics in burn patients and intravenous drug abusers. Antimicrob. Agents Chemother. **34:**792–795.
28. **Rybak, M. J., E. M. Bailey, K. C. Lamp, and G. W. Kaatz.** 1992. Pharmacokinetics and bactericidal rates of daptomycin and vancomycin in intravenous drug abusers being treated for gram-positive endocarditis and bacteremia. Antimicrob. Agents Chemother. **36:**1109–1114.
29. **Schadd, U. B., G. H. McCracken, and J. D. Nelson.** 1980. Clinical pharmacology and efficacy of vancomycin in pediatric patients. J. pediatr. **96:**119–126.
30. **Schentag, J. J., D. E. Nix, and M. H. Adelman.** 1991. Mathematical examination of dual individualization principles (I): relationships between AUC above MIC and area under the inhibitory curve for cefmenoxime, ciprofloxacin, and tobramycin. DICP Ann. Pharmacother. **25:**1050–1057.
31. **Smith, I. L., and J. J. Schentag.** 1984. Noncompartmental determination of the steady-state volume of distribution during multiple dosing. J. Pharm. Sci. **73:**281–282.
32. **Sorrell, T. C., D. R. Packham, S. Shanker, M. Foldes, and R. Munro.** 1982. Vancomycin therapy for methicillin-resistant *Staphylococcus aureus*. Ann. Intern. Med. **97:**344–350.
33. **Stratton, C. W.** 1987. The role of the microbiology laboratory in the treatment of infective endocarditis. J. Antimicrob. Chemother. **20**(Suppl. A)**:**41–49.
34. **Thomas, F., P. Michel, and Y. Ravaud.** 1988. Treatment of staphylococcal infections in adults by continuous intravenous infusion of vancomycin as single drug therapy. Sem. Hop. Paris **65:**215–218.
35. **Watanakunakorn, C.** 1981. The antibacterial action of vancomycin. Rev. Infect. Dis. **3:**S210–S215.
36. **Weinstein, M. P., C. W. Stratton, A. Ackley, H. B. Hawley, P. A. Robinson, B. D. Fisher, D. V. Alcid, D. S. Stephens, and L. B. Reller.** 1985. Multicenter collaborative evaluation of a standardized serum bactericidal test as a prognostic indicator in infective endocarditis. Am. J. Med. **78:**262–269.
37. **Zimmermann, A. E., B. G. Katona, and K. I. Plaisance.** 1995. Association of vancomycin serum concentrations with outcomes in patients with gram-positive bacteremia. Pharmacotherapy **15:**85–91.