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Vancomycin for *Staphylococcus aureus* Endocarditis in Intravenous Drug Users

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The clinical courses of 13 consecutive intravenous drug users with *Staphylococcus aureus* endocarditis treated principally with vancomycin were reviewed. Two patients, one with only right-sided endocarditis and the other with tricuspid and mitral valve endocarditis, had recurrences of positive blood cultures 2 days after completing a 4-week course of vancomycin. Two patients, both of whom eventually were cured, had modifications of therapy because of bacteremia persisting 7 and 16 days into therapy. One patient required an operation for recurrent fevers, and the resected vegetation showed evidence of active infection. Time-kill studies performed with nafcillin and vancomycin for 10 isolates of *S. aureus* showed that vancomycin was less rapidly bactericidal than nafcillin. Although vancomycin is used as an alternative to penicillinase-resistant penicillins for treatment of staphylococcal endocarditis, these findings raise the question of whether it is equivalent to these drugs in efficacy.

Staphylococcus aureus endocarditis in parenteral drug users is well characterized; complications and relapses are unusual. Overall cure rates of 95% are expected (3, 6, 17). This excellent cure rate partly is due to the fact that in three-quarters of cases the tricuspid valve, rather than aortic or mitral valves, is the site of infection. Bacteremia is rapidly cleared, lasting a mean of 3.4 days when nafcillin alone is used (17).

Vancomycin is often considered equal in efficacy to penicillinase-resistant beta-lactam antibiotics. However, a review of our experience in treating *S. aureus* endocarditis in intravenous drug users with vancomycin revealed unsatisfactory or unexpectedly complicated clinical courses in 5 of 13 cases (38%). These cases are summarized and the current literature pertaining to the efficacy of vancomycin for *S. aureus* endocarditis is reviewed below.

MATERIALS AND METHODS

Patients. The names of all patients admitted to San Francisco General Hospital with blood cultures growing *S. aureus* were collected prospectively from records of the clinical microbiology laboratory. Intravenous drug users with community-acquired *S. aureus* bacteremia treated primarily with vancomycin were identified for July 1983 through July 1987.

The medical records of these cases were reviewed to identify patients with endocarditis. Patients were considered to have endocarditis if they had (i) a temperature greater than 38.5°C, (ii) cardiac murmurs, (iii) at least two blood cultures growing only *S. aureus* without any obvious extracardiac source of bacteremia, and (iv) one or more of the following: physical findings of peripheral emboli, chest X rays consistent with septic pulmonary infiltrates, and valvular vegetations on echocardiograms. For cases in which auscultatory or echocardiographic findings did not identify the infected valves, the presence of pulmonary involvement or peripheral emboli was used to define right- or left-sided involvement, respectively.

Drug users with *S. aureus* endocarditis whose primary antibiotic was vancomycin were identified, and their responses to treatment were reviewed. The response to vancomycin was defined as unsatisfactory (i) if persistent bacteremia leading to an alteration in therapy had occurred or (ii) if relapse was observed. Patients who responded to therapy with prompt defervescence and sterilization of blood cultures and who were clinically well at the time of discharge were considered cured. No information about late relapse rates after discharge was obtained since most patients were lost to follow-up.

Laboratory studies. *S. aureus* isolates from intravenous drug users with endocarditis were obtained from the clinical laboratory. Four strains were from the five patients who had unsatisfactory clinical responses to vancomycin. MICs of vancomycin and nafcillin were determined by the tube macrodilution method. Serial twofold dilutions of antibiotic in Mueller-Hinton broth supplemented with calcium (50 mM) and magnesium (20 mM) (CSMHB) were inoculated with 3×10^5 log-phase CFU/ml. The tubes were incubated at 37°C for 18 h. The MIC was defined as the lowest concentration of antibiotic resulting in inhibition of bacterial growth as measured by visual turbidity. The MBC, determined by culturing 10 μl from each clear tube onto blood agar and incubating overnight at 37°C, was defined as the concentration which had reduced the original inoculum by 99.9%.

Time-kill studies were performed with 10 ml of CSMHB with an inoculum of 10^7 log-phase CFU/ml. To the respective cultures was added no drug, vancomycin, or nafcillin at a concentration four times the MIC for the strain. Cultures were then incubated at 37°C in a shaking incubator. At 0, 4, and 24 h 0.1-ml samples were removed and quantitatively cultured. Studies were performed on two different occasions, with the same results each time.

RESULTS

Patients. Twenty-two intravenous drug users who were treated primarily with vancomycin for community-acquired *S. aureus* bacteremia were identified. Nine patients were excluded because they had obvious extracardiac sources of bacteremia and no evidence of endocarditis. The remaining 13 cases were reviewed.

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TABLE 1. Clinical data for patients with unsatisfactory responses to vancomycin

Patient no.	Age (yr)	Sex[a]	Valve[b]	Vancomycin concn in serum (μg/ml)[c]	Vancomycin MIC/MBC (μg/ml)	Outcome
1	47	M	TV	T = 2.9	1/2	Relapse after 29 days of therapy
2	30	F	TV	P = 16.8	2/16	Relapse after 28 days of therapy
			MV	T = 7.4		
3	33	M	TV	P = 28.2	1/4	Bacteremia for 16 days
				T = 15.8		
4	26	F	TV	P = 43	1/	Bacteremia for 7 days
			MV	T = 15		
5	37	M	TV	P = 26	1/2	Gram-positive cocci on valve after 37 days of therapy
				T = 9.2		

[a] F, Female; M, male.
[b] TV, Tricuspid valve; MV, mitral valve.
[c] T, Trough; P, peak.

Eight patients were males. Ages ranged between 26 and 47 years (mean, 33). Five patients had histories of prior episodes of endocarditis, and two others had known valvular pathologies. All strains were initially susceptible to vancomycin, aminoglycosides, and rifampin.

Of 13 patients, 8 had satisfactory responses to therapy with vancomycin. Both patients who were infected by methicillin-resistant *S. aureus* were cured. The mean (± standard deviation) peak concentration of vancomycin in serum was 25 ± 9 μg/ml (n = 6), and the range was 13 to 34 μg/ml. The mean trough concentration in serum was 9 ± 5 μg/ml (n = 7), and the range was 3.4 to 20 μg/ml.

Of the eight patients who responded satisfactorily, six had signs only of right-sided endocarditis. One patient had left-sided endocarditis involving the mitral valve, and one had bilateral endocarditis with aortic and tricuspid valve involvement. Six patients had valvular vegetations seen on echocardiogram.

Of 13 patients, 5 had either a relapse of endocarditis or a complicated clinical course suggestive of an unsatisfactory response to vancomycin. All five were infected with methicillin-susceptible *S. aureus* and were being treated with vancomycin because of penicillin allergies. The mean peak concentration of vancomycin in serum in these patients was 28 ± 11 μg/ml (n = 4), and the range was 17 to 43 μg/ml. The mean trough concentration in serum was 10 ± 5 μg/ml (n = 5), and the range was 2.9 to 16 μg/ml.

Three of these five patients had only right-sided endocarditis, and two had bilateral endocarditis with tricuspid and mitral valve involvement in both cases. Three patients had vegetations seen on echocardiogram. Details of the clinical courses for each of these five patients are given below. Patient 1 (Table 1) had only right-sided endocarditis. Every blood culture drawn during the first 10 days of therapy with vancomycin (1 g administered every 12 h as a single agent) was positive for *S. aureus*. Therefore, rifampin was added on day 11 and blood cultures were documented to be sterile 3 days later. A bone scan, abdominal computerized tomography, and an indium-labeled leukocyte scan showed no evidence of a metastatic focus of infection. After 29 days of vancomycin and 19 days of rifampin, antibiotics were stopped. Two days later fever recurred and multiple blood cultures were positive for a rifampin-resistant strain of *S. aureus*, which had an antibiotic susceptibility profile that was otherwise the same as that of the original isolate. An echocardiogram, which initially had shown no vegetations, revealed interval development of tricuspid valve vegetations. The patient was treated with ciprofloxacin, 750 mg orally twice daily, for 6 days. Because blood cultures remained positive, therapy was changed to nafcillin and tobramycin. Blood cultures were sterile 3 days later, and the patient was cured after 48 days.

Patient 2, a 30-year-old woman with tricuspid and mitral valve endocarditis, was treated initially with 600 mg of vancomycin every 8 h plus tobramycin (1 mg/kg of body weight every 8 h for the first 8 days). Blood cultures were sterile on day 8 of treatment. Therapy was stopped after a total of 28 days of vancomycin. Two days later fever recurred and multiple blood cultures again grew the same β-lactamase-negative strain of *S. aureus* as the original isolate. An extensive evaluation revealed no extracardiac focus of infection. Vancomycin and gentamicin were restarted. Blood cultures remained positive after 11 days, so rifampin was added. Four days later all cultures were sterile. The patient was cured with this second course of vancomycin and gentamicin for 53 days and rifampin for 43 days.

Patient 3, who has been reported in a previous publication (6), was a 33-year-old male admitted with uncomplicated right-sided endocarditis. An echocardiogram showed no vegetation. Blood cultures remained positive after 16 days of vancomycin (1 g every 12 h) plus tobramycin (1 mg/kg of body weight every 8 h). Tobramycin was discontinued and rifampin was added, and 7 days later blood cultures were sterile. Because of persistent fevers, vancomycin was discontinued and nafcillin and tobramycin were begun. The patient eventually was cured.

Patient 4 was a 26-year-old woman with tricuspid and mitral valve vegetations who remained bacteremic after 7 days of vancomycin, 500 mg every 6 h. Rifampin was added, and subsequently blood cultures became sterile. Fever persisted for 25 days. After 29 days, the patient was discharged against medical advice but was clinically well and was lost to follow-up.

Patient 5, a 37-year-old man, had right-sided endocarditis with a pedunculated vegetation present on the tricuspid valve by echocardiography. This patient was initially treated with nafcillin and tobramycin and became afebrile. Because of indocin-induced acute renal failure, treatment was changed to vancomycin on day 4. On hospital day 12, fevers recurred. Even though blood cultures were negative, cefazolin was begun on day 16 and was continued for 12 days. The patient was discharged on oral cephradine but returned 8 days later with myalgia, fevers, and a newly elevated erythrocyte sedimentation rate. Multiple blood cultures were negative. Vancomycin was restarted. Because of persistent fevers after 8 days, an operation to remove the tricuspid valve vegetation was performed. Pathologic examination of the vegetation showed acute inflammation and gram-positive

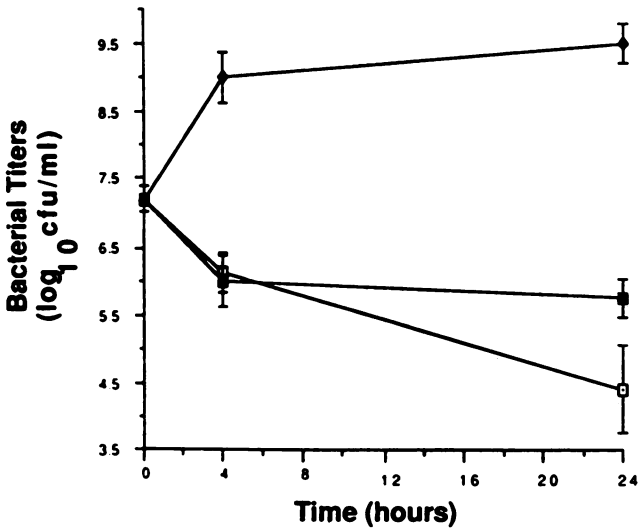

FIG. 1. Time-kill curves for nafcillin (□) and vancomycin (■) at a concentration of four times the MIC for 10 clinical isolates of *S. aureus*. ◆, Control.

cocci, but cultures were negative. His postoperative recovery was unremarkable, and he was cured with an additional 20 days of vancomycin.

Laboratory studies. The geometric mean MICs of vancomycin and nafcillin were 1.0 and 0.5 μg/ml, respectively, against 10 strains of *S. aureus* isolated from intravenous drug users with endocarditis. Geometric mean MBCs were 5 μg/ml for vancomycin and 16 μg/ml for nafcillin.

MICs for four strains from patients who had unsatisfactory responses to vancomycin did not differ from those for the other strains. MBCs for these four strains compared with the others also were similar, with geometric means of 4 and 5 μg/ml, respectively. No strains were tolerant.

At four times the MIC, vancomycin was less rapidly bactericidal than nafcillin (Fig. 1). After 4-h incubation the mean decreases in bacterial counts for nafcillin and vancomycin were similar (1.1 and 1.2 $\log_{10}$ CFU reductions in inoculum per ml, respectively). After 24 h, the mean count for vancomycin had not significantly changed from that at 4 h (reduction of 1.4 $\log_{10}$ CFU/ml from the initial inoculum; $P > 0.05$ by analysis of variance) compared with a significant reduction in counts after 24 h for nafcillin (2.8 $\log_{10}$ CFU/ml; $P < 0.001$). The four strains from patients with unsatisfactory responses behaved no differently from the six other strains.

DISCUSSION

Intravenous drug users with *S. aureus* endocarditis, in whom the tricuspid valve is most often infected, almost always respond to antibiotics (3). Persistent bacteremia, relapse, and death are unusual.

Table 2 summarizes the results of treatment of more than 300 cases of *S. aureus* endocarditis in drug users (1, 6, 7, 12, 14, 17, 22–24, 26, 27). Although methodologies and definitions of failure may differ among studies, limiting direct comparison of results, rates of unsatisfactory outcomes can be estimated when results of these studies are combined. Clinical failure was reported in less than 2% of the cases, and only 20 of 362 (6%) patients died or had a relapse. In selected patients with right-sided *S. aureus* endocarditis, just 2 weeks of nafcillin and tobramycin gives a relapse rate of 6% (6).

TABLE 2. Response to treatment of *S. aureus* endocarditis in intravenous drug users

Study (reference)	No. (%) of clinical failures[a]	No. (%) of relapses	No. (%) of deaths
Abrams et al. (1)	0/25 (0)	0/25 (0)	0/25 (0)
Chambers et al. (6)	0/50 (0)	3/50 (6)	0/50 (0)
Cooper et al. (7)	0/11 (0)	0/11 (0)	0/11 (0)
Greenman et al. (14)	1/32 (3)	4/32 (12)	0/32 (0)
Korzeniowski et al. (17)	0/48 (0)	1/48 (2)	1/48 (2)
Menda and Gorbach (20)	2/16 (12)	1/16 (6)	0/16 (0)
Parker and Fossieck (22)	0/31 (0)	0/31 (0)	0/31 (0)
Rajashekaraiah et al. (23)	NE[b]	0/38 (0)	3/38 (12)
Sklaver et al. (24)	NE	1/55 (0)	0/55 (0)
Tuazon et al. (26)	NE	1/40 (2)	3/40 (8)
Weinstein et al. (27)	NE	2/16 (12)	0/16 (0)
Total	3/213 (1.4)	13/362 (3.6)	7/362 (2)

[a] Defined as an adjustment in therapy because of unsatisfactory clinical or bacteriologic response.
[b] NE, Not evaluable from data presented in the study.

An unsatisfactory response in 5 of 13 (38%) intravenous drug users with *S. aureus* endocarditis who were treated with vancomycin is remarkable. Two patients of the five did have left-sided involvement, which probably made their infections more difficult to treat. However, three patients had only right-sided endocarditis, from a total of nine patients with right-sided endocarditis in the study.

Anecdotal reports suggest that vancomycin failures may not be uncommon for endocarditis caused by *S. aureus*. Geraci and Wilson (11) reported 12 patients with left-sided *S. aureus* endocarditis; treatment with vancomycin alone failed for five (42%), requiring combination therapy for cure, and one patient with prosthetic valve endocarditis died during vancomycin therapy.

In numerous case reports (2, 8, 10, 13, 19; J. G. Morris and J. H. Tenney, Letter, Ann. Intern. Med. **99**:283–284, 1983), patients have not been cured with vancomycin alone, whereas combinations, often including rifampin, have been effective. Even the combination of vancomycin and rifampin may not always be effective (9).

Vancomycin treatment for methicillin-resistant endocarditis also suggests that results with vancomycin may be less satisfactory than is expected with beta-lactam antibiotics for methicillin-susceptible *S. aureus* (9). A 28-day course of vancomycin was adequate for most patients, and a cure rate of 80% was cited. If the 17 patients who completed medical therapy (excluding 2 patients who underwent surgery and the 5 who left the hospital against medical advice) are analyzed, then there were 2 deaths, no relapses, and 4 clinical failures requiring the use of additional antibiotics, for unsatisfactory responses in 6 of 17 patients (35%).

In this series endocarditis clearly recurred in two patients after what should have been an adequate 4-week course of vancomycin. In both patients, the maximum recommended 2-g (or 30 mg/kg of body weight) daily dose of vancomycin was being used. In patient 1, who had only right-sided endocarditis, the trough vancomycin concentration of approximately 3 μg/ml was low even at this dose. On the other hand, he was receiving rifampin, and serum approximately 1 h after a dose of vancomycin was bactericidal at a dilution of 1:16. Perhaps vancomycin clearance was increased in this patient, and, despite apparently adequate bactericidal activity at the peak concentration in serum, vancomycin concentrations may have been subtherapeutic much of the time thereafter. When dosing vancomycin, therefore, it might be

better to target peak and trough concentrations in serum rather than to adhere to strict dosage guidelines (12).

Vancomycin also failed to cure endocarditis in patient 2. Attributing failure solely to vancomycin is difficult, however, because this patient had both right- and left-sided endocarditis, which is a much more complicated infection to treat. Nevertheless, a 4-week course of antibiotics still would be expected to be curative. The persistence of positive blood cultures for 11 days during treatment of the relapse with vancomycin and gentamicin was exceptional.

Patients 3 (who was receiving both vancomycin and tobramycin) and 4 were eventually cured, but both had prolonged bacteremia (16 and 7 days, respectively) prompting the addition of other antibiotics. Given that nafcillin alone clears the bacteremia of staphylococcal endocarditis with a mean of 3.4 days (17), the durations of bacteremia in these cases were notable.

Whether vancomycin was ineffective in patient 5 is impossible to know for sure. This patient was treated with several antibiotics besides vancomycin. Persistent fever, although not specific for drug failure, was perceived as indicating a lack of response to vancomycin and led to use of cefazolin. Vancomycin still was the primary agent in this case. Because of renal failure, therapeutic concentrations of vancomycin in serum were present for approximately 23 days of the 37 total treatment days before surgery. Persistent fever, surgery in the setting of right-sided staphylococcal endocarditis, and the presence of gram-positive cocci in the vegetation suggest that vancomycin was ineffective.

The reasons some of our patients responded and others did not are unclear. Vancomycin concentrations in serum were virtually identical in each group. Three of five versus six of eight patients had right-sided endocarditis only. Echocardiographic findings were similar.

In vitro vancomycin was less rapidly bactericidal than nafcillin. Although data are limited, vancomycin was less rapidly bactericidal in a rat model of endocarditis (5). Vancomycin may be relatively less rapidly bactericidal in human endocarditis as well. This could explain the relapses and persistent bacteremia observed in this study and may account for the relatively long period of bacteremia (7 days) reported by others (18).

Previous studies reporting efficacy of vancomycin have concentrated on pulmonary, intravenous catheter, or soft tissue infections (4, 16, 25). Vancomycin may be less effective for endocarditis because of the need for prolonged high levels of bactericidal antibiotics. The fact that vancomycin was less rapidly bactericidal in vitro than nafcillin is consistent with our concern that vancomycin may be less effective than nafcillin for treating this infection.

The implications of these observations for clinicians treating staphylococcal endocarditis with vancomycin are unclear. This is a small retrospective review that is far from proving that vancomycin is less effective than beta-lactam antibiotics. A randomized, prospective comparison is needed to determine whether vancomycin is less effective than beta-lactam antibiotics.

Before labeling a patient as allergic to penicillin, it is important to document the nature of the allergy. Some patients who report mild allergic reactions to penicillin can tolerate a full course of nafcillin. In patients who are truly allergic to penicillin, few alternatives to the use of vancomycin currently are available. When vancomycin is used, particular attention should be given to the possibility of clinical failure, even if a prompt response is suggested by resolution of fever and sterilization of blood cultures. The addition of aminoglycosides or rifampin has been shown to be efficacious in some cases (15, 21). However, in this study patients who were not responding satisfactorily were receiving antibiotic combinations. Further studies to identify effective alternatives to vancomycin for serious *S. aureus* infections are needed.

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