ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1986, p. 209–211
0066-4804/86/020209-03$02.00/0

Vol. 29, No. 2

Persistent Staphylococcal Bacteremia in an Intravenous Drug Abuser

NEIL L. BARG,[1]†* RONALDO B. SUPENA,[2] AND ROBERT FEKETY[1]

Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Hospitals, Ann Arbor, Michigan 48109,[1] and Wayne County General Hospital, Westland, Michigan 48185[2]

Received 2 July 1984/Accepted 10 November 1985

A patient with methicillin-resistant *Staphylococcus aureus* bacteremia received vancomycin (MIC = 0.8 μg/ml, MBC = 15 μg/ml) and heparin simultaneously through the same intravenous line to treat a septic deep venous thrombosis. Bacteremia persisted for 7 days. Bacteremia terminated when the simultaneous infusion of heparin and vancomycin through the same line was stopped. This suggested that an interaction between vancomycin and heparin may have occurred, which resulted in a reduction in vancomycin activity. To test for such an interaction, mixtures of heparin and vancomycin in various concentrations were made and tested for antimicrobial activity against the organisms in the patient. A precipitate formed at the concentrations achieved in the intravenous lines, and when the vancomycin concentrations were measured by bioassay, a 50 to 60% reduction in activity was noted. In contrast, when these solutions were prepared and mixed at microgram concentrations, a precipitate was no longer observed, and antimicrobial activity was not reduced. Heparin appeared to interact unfavorably with vancomycin at the concentrations in the intravenous lines when these drugs were administered simultaneously to patients. This may be the cause of poor therapeutic responses to vancomycin in some patients, especially those infected with tolerant organisms.

Among the causes of persistent or breakthrough bacteremia are a removable focus of infection, an incorrect choice or dosage of antibiotics, an undrained abscess, and an incorrect mode of drug administration. A case of persistent staphylococcal bacteremia was observed at our hospital. Persistence of the organism may have resulted from antibiotic inactivation because of simultaneous administration of heparin and vancomycin through the same intravenous line. This may have caused a chemical or physical reaction that resulted in some nullification of the antibacterial activity of vancomycin. This phenomenon has not been described previously for vancomycin and heparin, but Ragamey et al. have described decreased aminoglycoside activity when gentamicin was exposed to heparin in blood-sampling tubes (6). Vancomycin and heparin are known to be incompatible, probably because of a concentration-dependent acid-base reaction causing a precipitate in material (8) prepared in 5% dextrose for intravenous use.

Because of the high frequency of deep femoral vein thrombosis occurring with femoral vein drug injection, and also because of the frequency of methicillin-resistant *Staphylococcus aureus* bacteremia in drug abusers, heparin and vancomycin are often administered concomitantly. If the activity of vancomycin is decreased when mixed with heparin, a poor clinical outcome is possible for many of these patients. We report a patient in whom this may have occurred.

CASE REPORT

A 33-year-old male from Detroit was admitted to the Wayne County Hospital because of fever and right groin pain. The patient admitted to using heroin intravenously for the past 3 years; usually he injected it into the femoral veins. He often self-administered oral cephalexin concomitantly. Two days before admission he noted fever, shaking chills, and diaphoresis. He also noted swelling and tenderness of the right groin at the injection site. His temperature was 102°F (38.9°C), and he had a tender, indurated area overlying the right femoral triangle. No peripheral signs of endocarditis were observed, but there was a grade II/VI systolic ejection murmur noted at the lower left sternal border that increased with inspiration.

Since no peripheral venous access was available, a subclavian venous line was placed with a sterile technique. The patient was empirically treated with 1.0 g of vancomycin intravenously in 250 ml of 5% dextrose every 12 h (infused over 30 min) and with 90 mg of tobramycin intravenously every 8 h. Cultures of blood and of a subcutaneous aspirate from the right femoral triangle grew methicillin-resistant *S. aureus*. Tobramycin was discontinued once *S. aureus* was identified as the infecting organism (vancomycin MIC = 0.8 μg/ml, MBC = 15 μg/ml). Shortly after his admission, a venogram was performed and confirmed the suspicion of a deep venous thrombosis. A continuous infusion of heparin (25,000 U/day) in 1,000 ml of 5% dextrose was administered. Both heparin and vancomycin were infused through the same line. Fever persisted, and blood cultures remained positive for methicillin-resistant *S. aureus* for 7 days. No signs of cardiac vegetations were found on a two-dimensional echocardiogram. No area of fluctuance developed in the right femoral triangle. The serum creatinine did not rise above 1.2 mg/dl during hospitalization. After 7 days another intravenous line was started, and the vancomycin and heparin were infused through separate lines at the identical dosage and frequency as before. Within 24 h the patient became afebrile, and subsequent blood cultures were negative (Fig. 1). The patient was discharged afebrile after

* Corresponding author.
† Present address: Division of Infectious Diseases, St. Thomas Hospital, Nashville, TN 37202.

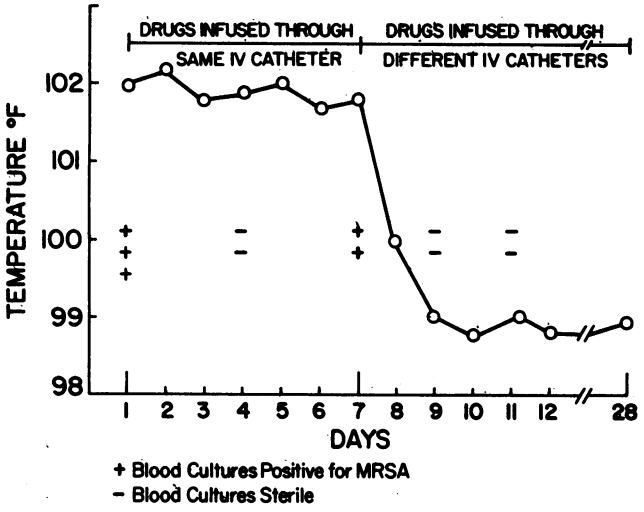

FIG. 1. Relationship of daily body temperatures (O) and positive blood cultures to method of administration of heparin and vancomycin.

completing a 4-week course of vancomycin and was ultimately lost to follow-up.

MATERIALS AND METHODS

The presumed alteration in the activity of vancomycin by heparin was tested by dissolving vancomycin in 250 ml of 5% dextrose to yield a concentration of 4 mg/ml; heparin was mixed with 1 liter of 5% dextrose solution to yield a concentration of 25 U/ml. These concentrations were equivalent to those in the intravenous line when vancomycin and heparin were administered to the patient simultaneously. A solution of vancomycin (4 mg/ml) alone and a solution of heparin (25 mg/ml) plus vancomycin (4 mg/ml) were immediately diluted serially with human serum (AB positive) to provide various concentrations of each drug within the range of a bioassay system. The final calculated vancomycin concentrations ranged from 2.5 μg/ml to 100 μg/ml, and the final heparin concentrations ranged from 0.01 to 0.625 U/ml. Serum was used to simulate the conditions when a mixture of vancomycin and heparin is infused intravenously. Aliquots (20-μl) of the various dilutions were added to standard diffusion disks, which were dropped onto agar (antibiotic medium 5; Difco Laboratories, Detroit, Mich.) that had been inoculated with *Bacillus subtilis*. After plates were incubated for 4 h at 35°C, zone diameters were measured and compared with the zones around known concentrations of vancomycin (1).

When administered through separate intravenous lines, high concentrations of vancomycin and heparin do not mix. Each drug is diluted within the intravascular space to much lower concentrations before their contact. Gradient plates were prepared for an assay of the vancomycin activity of the solutions that were initially prepared at these lower concentrations (2 to 25 μg/ml) expected in the serum of patients (7). Vancomycin, at concentrations of 2, 4, 5, 6, and 25 μg/ml, was mixed with heparin at a concentration of 0.5 U/ml, added to Mueller-Hinton agar, poured into inclined square plates, and allowed to harden. This mixture was prepared from solutions that were not permitted to mix at high concentrations. After returning plates to a horizontal position, plain Mueller-Hinton agar was added to level off the top of each plate. Similar plates were prepared without heparin. Overnight broth cultures of three methicillin-resistant *S. aureus* strains (vancomycin MICs and MBCs were 1.6 and 1.6, 3.1 and 3.1, and 6.25 and 6.25 respectively) were streaked with a cotton-tipped applicator in the axis of the concentration gradient and incubated at 35°C overnight. The physical length of the colony growth was measured and compared with the length of colonies in similar plates containing vancomycin alone. The MIC and MBC for all organisms were determined by the microtiter technique described by Harwick et al. (4).

TABLE 1. Effects of heparin upon vancomycin concentrations as measured by bioassay

Calculated concn[a] for:		Observed vancomycin concn without heparin (μg/ml)[b]	Observed vancomycin concn with heparin (μg/ml)[b]	Reduction from calculated vancomycin concn (%)[c]
Heparin (U/ml)	Vancomycin (μg/ml)			
0.625	100	100	45	55
0.313	50	60	22	56
0.156	25	29	14	44
0.125	20	21	11.5	42
0.078	12.5	17.5	7.5	40
0.063	10	15	6.25	37.5
0.031	5	9.5	3.4	32
0.016	2.5	4.6	1.8	28

[a] A mixture of 4 mg of vancomycin per ml of 5% dextrose plus 25 U of heparin per ml of 5% dextrose was diluted with human AB positive serum to make the calculated concentrations.

[b] Derived by comparing zone diameters of the assay solution compared to the zone diameters of standard disks containing known concentrations of vancomycin alone.

[c] Percentage by which the calculated levels of bioactive vancomycin was reduced in the observed levels of this agent mixed with heparin.

RESULTS

When the mixture of high concentrations of vancomycin (4 mg/ml) plus high concentrations of heparin (25 U/ml) in 5% dextrose was diluted to concentrations within the range of the bioassay system (vancomycin at 2.5, 5, 10, 12.5, 25, 50, and 100 μg/ml and heparin at 0.01, 0.03, 0.06, 0.08, 0.16, 0.31, and 0.63 U/ml), the mean reduction in vancomycin activity was 42% (range, 28 to 56%). Vancomycin alone, prepared in a similar manner and diluted to the same

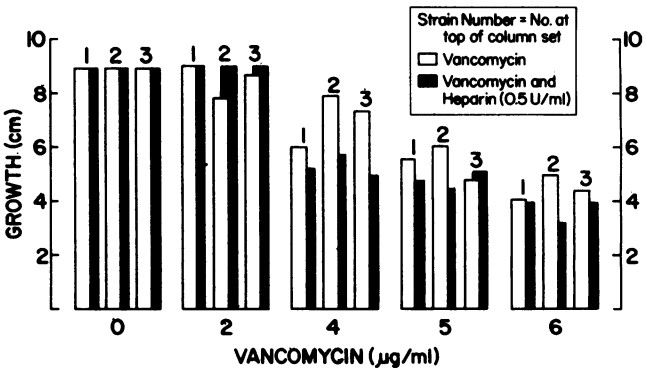

FIG. 2. Growth of three methicillin-resistant *S. aureus* strains on gradient plates with low concentrations of vancomycin and of vancomycin and heparin.

concentrations, showed no reduction in bioactivity (Table 1).

In contrast, the gradient plate assay showed no significant difference between the antibacterial effects of vancomycin alone in agar and of vancomycin mixed with heparin at much lower initial concentrations (2 to 25 μg/ml and 0.5 U/ml, respectively) (Fig. 2). Therefore, there was no observed effect of heparin on the bioactivity of vancomycin when the mixture was initially prepared at the concentrations expected in serum after infusion of the two drugs through separate intravenous lines.

At the higher concentrations that probably occur in intravenous tubing when the two drugs are infused simultaneously (1 to 5 mg of vancomycin per ml and 1 to 1,000 U of heparin per ml), a white precipitate was immediately noted in tubes containing both vancomycin and heparin. On the other hand, at concentrations attainable in serum (vancomycin at 5, 50, and 100 μg/ml and heparin at less than 1 U/ml), no precipitates formed.

DISCUSSION

The staphylococcal bacteremia persisting for 7 days in this patient was unusual and was presumably caused by inactivation of vancomycin by heparin in mixtures of the two agents in a single intravenous line. Korzeniowsky and Sande report that the mean duration of methicillin-susceptible staphylococcal bacteremia is 3 days (±1 day) in addicts with right-sided endocarditis treated with nafcillin and gentamicin (5). The diminished activity of vancomycin coupled with the relatively high MBC (tolerance) for this isolate may have prevented in vivo killing of the organism. Typical peak concentrations of vancomycin in serum after a 1-g intravenous dose are between 20 and 50 μg/ml (2). However, if a 50 to 60% reduction in the bioactivity of vancomycin occurs after reacting with heparin, the net bioactive vancomycin in the serum may be as low as 8 μg/ml. The usual MICs of vancomycin for methicillin-susceptible *S. aureus* range from 1.56 to 3.12 μg/ml (3). MICs and MBCs for methicillin-resistant *S. aureus* in our laboratory are similar to those of methicillin-susceptible *S. aureus*, with MICs and MBCs ranging from 0.4 to 6.25 μg/ml. It is possible that the quantity of bioactive vancomycin was insufficient to kill the organism isolated from this patient. The vancomycin-heparin interaction probably occurred within the same intravenous tubing during administration of the compounds that were allowed to mix at high concentrations. Once concomitant administration of the two drugs through one intravenous line ceased and additional vancomycin was infused, bacteremia ceased. Unfortunately, concentrations of vancomycin were not measured in the serum when the two drugs were infused through the same line, so the precise effect of mixing the two drugs upon the bioactivity of vancomycin in the serum of our patient could not be determined.

The incompatibility of vancomycin and heparin prepared in dextrose-and-water solutions is well known. In 0.9% sodium chloride solutions, the two drugs are more compatible. It has been suggested that when the two drugs need to be administered through the same intravenous line, the solution should be prepared in 0.9% sodium chloride (8). Because of the frequent occurrence of deep venous thrombosis and methicillin-resistant *S. aureus* bacteremia in the intravenous drug abuser population, care should be taken to avoid administration of heparin and vancomycin through the same intravenous line. Vancomycin, in addition, is often administered to renal dialysis patients through a heparinized fistula. Studies are planned to determine if vancomycin is inactivated in this situation.

The gradient plate assay showed no significant effect of heparin on vancomycin activity at the usual serum concentrations. No alteration in the bioactivity of vancomycin would be expected, therefore, when heparin in infused through a separate intravenous line. Once diluted in the intravascular space after separate infusion of each drug, the concentration of both drugs is much lower, in the range tested by the gradient plate assay. If necessary, infusion of the two drugs through the same line could be done serially, with a 0.9% sodium chloride solution flushing the line between the two drugs to prevent mixing at high concentration.

LITERATURE CITED

1. **Edberg, S. C, and L. D. Sabath.** 1980. Determination of antibiotic levels in body fluids: techniques and significance. Bactericidal tests in endocarditis and other severe infections, p. 206–264. *In* V. Lorain (ed.), Antibiotics in laboratory medicine. The Williams & Wilkins Co., Baltimore.
2. **Fekety, F. R.** 1985. Vancomycin, p. 232–235. *In* G. L. Mandell, R. G. Douglas, Jr., and J. R. Bennett (ed.), Principles and practice of infectious diseases. John Wiley & Sons, Inc., New York.
3. **Geraci, J. E., and P. E. Hermans.** 1983. Vancomycin. Mayo Clin. Proc. **58**:8–91.
4. **Harwick, H., P. Weiss, and F. R. Fekety.** 1968. Application of microtitration techniques to bacteriostatic and bactericidal antibiotic susceptibility testing. J. Lab. Clin. Med. **72**:511–516.
5. **Korzeniowski, O., M. A. Sande, and the National Collaborative Endocarditis Study Group.** 1982. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts. Ann. Intern. Med. **97**: 496–503.
6. **Regamey, C., D. Schaberg, and W. M. M. Kirby.** 1972. Inhibitory effect of heparin on gentamicin concentrations in blood. Antimicrob. Agents Chemother. **1**:329–332.
7. **Sherris, J. C., and B. H. Minshew.** 1980. Mutational antibiotic resistance, p. 418–432. *In* V. Lorian (ed.), Antibiotics in laboratory medicine. The Williams & Wilkins Co., Baltimore.
8. **Trissel, L. A. (ed.).** 1981. Handbook on injectable drugs, 2nd ed., p. 255–258, 538–541. Elsevier Biomedical Press, Amsterdam.