Stability of Antibiotics Used for Antibiotic-Lock Treatment of Infections of Implantable Venous Devices (Ports)

THIELE UMALI ANTHONY AND LORRY G. RUBIN*

Division of Infectious Diseases, Department of Pediatrics, Schneider Children’s Hospital of Long Island Jewish Medical Center, the Long Island Campus for the Albert Einstein College of Medicine, New Hyde Park, New York 11040

Received 6 November 1998/Returned for modification 22 April 1999/Accepted 3 June 1999

Antibiotic-lock is a treatment for catheter-related bloodstream infections in which a solution containing heparin and an antibiotic dwells in the lumen of the catheter or port. We tested the stability of vancomycin, cefazolin, ticarcillin-clavulanic acid, ceftazidime, or ciprofloxacin combined with heparin after incubation in vitro at 25 or 37°C for intervals of up to 10 days by bioassay. All the antibiotic solutions except ceftazidime retained ≥90% activity at both 25 and 37°C. Thus, studies of antibiotic-heparin lock solutions with dwell times of up to 10 days are feasible.

There are two types of tunneled silastic central venous catheters commonly used for long-term venous access: Broviac-Hickman-type catheters and the totally implantable venous-access devices (ports). Catheter-related bloodstream infection of such catheters is an important cause of patient morbidity and premature catheter removal. Such infections commonly originate in the hub of the catheter (or access needles of ports) and reach the bloodstream via the interior lumen of the catheter (14). An attempt to treat bloodstream infections related to such catheters is often attempted with a 7- to 21-day course of systemic antibiotics administered through the catheter without catheter removal. Overall, a 75 to 80% success rate has been reported with both Broviac-Hickman-type catheters and ports, without catheter removal, although cure rates vary with the pathogen (3, 5, 7, 13, 15). Although treatment of catheter-related bloodstream infection with systemic antibiotics is frequently successful, there are drawbacks to this approach. At least 20% of treatments fail, resulting in device removal. Systemic antibiotic therapy often results in prolonged hospitalization, with the attendant expense, exposure to nosocomial infection, potential toxicity of systemic antibiotic therapy, and potential for infection with antibiotic-resistant bacteria or with yeast and fungi.

A new method of treating catheter-related infection, devised by Messing et al. (11), is called the antibiotic-lock technique (ALT). The method involves instilling an antibiotic-heparin solution in the lumen of the catheter and allowing it to dwell continuously for periods of 12 to 24 h, with a change in the lock solution at least every 24 h. This method delivers a small absolute amount of antibiotic to the patient but achieves a high local concentration in the catheter lumen that is 100 to 5,000 times higher than the MIC for the infecting bacterium. This local antibiotic therapy has been used either alone or as a follow-up to a short course of systemic antibiotics and has been shown to decrease catheter colonization with Staphylococcus epidermidis in vitro (4). ALT is a logical method of treating the large subgroup of catheter-related bloodstream infections in which the source of bloodstream bacteria is the catheter (or port) lumen (13). In noncomparative studies, this method has been used to treat catheter-related bloodstream infections with Broviac-Hickman-type catheters and ports and has shown promising results (1, 8–10, 12). In contrast to Broviac-Hickman-type catheters, which routinely require daily flushing and a lock with a heparin solution, ports require only monthly heparin flushing when they are not being accessed. In order to use the ALT with ports, daily instillation of the antibiotic-lock solution requires continuous or daily needle access to the device. In this study we tested the in vitro stabilities of five antibiotic-heparin solutions potentially useful for the ALT to determine if a dwell time of antibiotic-lock solutions longer than 24 h is feasible. This longer dwell time would allow for studies of the treatment of port-related infections with less frequent access.

Standard clinical powders of vancomycin (Eli Lilly & Co., Indianapolis, Ind.), cefazolin (Eli Lilly & Co.), ticarcillin-clavulanic acid (SmithKline Beecham Pharmaceuticals, Philadelphia, Pa.), and ceftazidime (Eli Lilly & Co.) were hydrated and diluted in sterile water and mixed with an equal volume of heparin (100 U/ml in saline) to achieve a final concentration of 500 μg/ml. Ciprofloxacin (Bayer Corporation, West Haven, Conn.) was tested at a concentration of 125 μg/ml because macroscopic precipitation was noted at higher concentrations. Antibiotic-heparin solutions were placed in sterile polystyrene test tubes and incubated at 25 or 37°C. In parallel experiments, groups of test tubes with each antibiotic-heparin solution were prepared and a final concentration of 10^4 CFU of a susceptible bacterial species per ml was added. Overnight cultures of S. epidermidis ATCC 35983, Klebsiella pneumoniae ATCC 13883, and Escherichia coli ATCC 25922 in Trypticase soy broth were used as additives to antibiotic-heparin solutions containing vancomycin, cefazolin, and ticarcillin-clavulanic acid. Similarly, Pseudomonas aeruginosa ATCC 28854 was added to antibiotic-heparin solutions containing ceftazidime or ciprofloxacin.

Samples were assayed for antibiotic concentration by a bioassay using a disk diffusion method and a susceptible bacterium (2). The activities of the antibiotic solutions were assayed after incubation for 1, 3, 7, or 10 days by inoculating blank 6-mm-diameter paper disks (BBL, Becton Dickinson and Company, Cockeysville, Md.) with 0.01 ml of antibiotic solution or with 0.01-ml samples of serial dilutions of a freshly prepared antibiotic-heparin solution of known concentration and allowing the disks to air dry. With a cotton swab moistened in a suspension of bacteria in Trypticase soy broth prepared from a fresh plate to the McFarland 0.5 standard, Mueller-Hinton II agar plates (BBL, Becton Dickinson and Company) were
streaked in three planes. Disks were aseptically transferred to the inoculated plates and incubated overnight. Zones of inhibition were measured with a micrometer, and a standard curve was constructed to correlate zone size with antibiotic concentration by using the following antibiotic concentrations: 0.1, 0.25, 0.5, 1.0, and 2.5 mg of vancomycin per ml; 0.1, 0.25, 1.0, and 5 mg of cefazolin, ticarcillin-clavulanic acid, or ceftazidime per ml, and 5, 10, 50, and 100 μg of ciprofloxacin per ml. The antibiotic activity in the test sample was determined by fitting the mean zone of inhibition to the standard curve. Determination of the stabilities of the solutions was done in duplicate, and each daily measurement was performed with duplicate disks. Two independent sets of experiments with each antibiotic were performed.

Results of determinations of the stabilities of the antibiotic-lock solutions are shown in Table 1. Vancomycin, cefazolin, and ticarcillin-clavulanic acid at a concentration of 500 μg/ml and ciprofloxacin at a concentration of 125 μg/ml admixed with 100 U of heparin per ml had ≤10% decreases in activities at both 25 and 37°C. Cefazidime had a 28 to 36% decrease in activity after 7 days at 37°C. Inclusion of 10^4 CFU of susceptible bacteria per ml to the solutions did not alter the stability of any of the antibiotics at either temperature.

The ALT of treating catheter-related bloodstream infection requires the antibiotic to dwell in the lumen of the catheter or port. This study demonstrated that vancomycin, cefazolin, ticarcillin-clavulanic acid, and ciprofloxacin, which collectively have activities against the vast majority of bacteria causing catheter-related bacteremias, retain >90% of their activities at either 25 or 37°C for 10 days. Although cefazidime lost up to 50% of its activity after 10 days at 37°C, the residual activity would be many times the MICs of the bacteria being treated; ceftazidime may be an adequate choice for dwell times of up to 7 days. We tested the solutions at different temperatures because different parts of the vascular catheter or port may be exposed to varying temperatures ranging from ambient to core body temperature. Our data showed that the solutions were stable at both temperatures for 7 days. We did not assay the stability of heparin under the same conditions. However, Henrikson and colleagues (6) evaluated the stability of the anticoagulant activity of heparin in combination with vancomycin at room temperature and at 4°C for periods of up to 6 weeks and found no loss of anticoagulant activity.

The concentrations we tested are similar to the concentrations that have been used clinically and provide an intraluminal concentration of ≥100 times the MICs of the relevant organisms with an extremely low antibiotic dose of ≤2 mg.

Although we have shown that it is likely that the antibiotic will retain bioactivity, it is unclear if the antibiotic will be retained in the catheter lumen or if it will be gradually siphoned into the body’s circulation. In assays of a limited number of samples, Benoit et al. (1) found 75 and 76% of initial vancomycin activity persisting at 4 and 8 to 12 h, respectively, after vancomycin lock installation and 46 and 62% of initial gentamicin activity persisting 4 and 8 to 12 h, respectively, after gentamicin lock installation. Thus, studies of the residual antibiotic activity of the lock solution that is removed from patients after dwelling for various durations are needed. In addition, it is possible that beta-lactamase production by a susceptible gram-negative bacillus is induced in the presence of the beta-lactam antibiotic used for ALT, resulting in antibiotic inactivation.

In summary, this study has demonstrated the stabilities of the antibiotics tested in the presence of heparin with or without a susceptible bacterium. These results provide the rationale for clinical studies of the duration of antibiotic activity in patients and the efficacy of antibiotic lock in the management of port-related bacteremias.

(This research was presented in part at the 35th Annual Meeting of the Infectious Disease Society of America, San Francisco, Calif., 13 to 16 September 1997.)

### REFERENCES


### TABLE 1. Effects of time, temperature, and the presence of bacteria on antibiotic bioactivities in antibiotic-heparin solutions

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Incubation temp (°C)</th>
<th>% of antibiotic activity remaining in antibiotic-heparin solutions (without/with addition of 10^4 CFU of bacteria/ml after an incubation^a of:</th>
<th>1 day</th>
<th>3 days</th>
<th>7 days</th>
<th>10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>25</td>
<td>100/100</td>
<td>97/100</td>
<td>99/100</td>
<td>98/95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>100/100</td>
<td>96/100</td>
<td>99/100</td>
<td>99/93</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>25</td>
<td>95/94</td>
<td>92/90</td>
<td>93/94</td>
<td>91/90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>97/95</td>
<td>94/90</td>
<td>90/90</td>
<td>91/91</td>
<td></td>
</tr>
<tr>
<td>Ticarcillin-clavulanate</td>
<td>25</td>
<td>100/100</td>
<td>100/100</td>
<td>100/99</td>
<td>96/96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>100/100</td>
<td>100/100</td>
<td>100/99</td>
<td>96/96</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>25</td>
<td>96/96</td>
<td>95/95</td>
<td>93/95</td>
<td>94/75</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>97/97</td>
<td>91/91</td>
<td>70/62</td>
<td>60/51</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>25</td>
<td>100/100</td>
<td>100/100</td>
<td>100/100</td>
<td>100/100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>100/100</td>
<td>100/100</td>
<td>100/100</td>
<td>100/100</td>
<td></td>
</tr>
</tbody>
</table>

^a Results are the means of results from two trials; results from each trial are the means of duplicate determinations from different disks. The first-listed percentage is the result in the absence of added bacteria and the second-listed percentage is the result in the presence of bacteria susceptible to the antibiotic tested.