Clindamycin Therapy of Experimental *Staphylococcus aureus* Endocarditis

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The efficacy of clindamycin in the treatment of experimental endocarditis in rabbits was compared with that of nafcillin. Both drugs were administered intramuscularly three times daily for 5 days, clindamycin at doses of 6.25, 12.5, 25, or 50 mg/kg and nafcillin at a dose of 200 mg/kg. The minimum inhibitory and bactericidal concentrations (0.125 μg/ml) of clindamycin for the test strain of *Staphylococcus aureus* were very similar to the corresponding concentrations (0.25 μg/ml) of nafcillin. The effectiveness of clindamycin against the experimental endocarditis was dose dependent. The therapeutic accomplishments of the two highest clindamycin doses were equivalent to those attained with 200 mg of nafcillin per kg. The rates of sterilization of vegetations were equal when the serum bactericidal titers of these drugs were ≥1:8. In special situations the administration of clindamycin in high doses could prove useful in the treatment of *S. aureus* endocarditis.

*Staphylococcus aureus* is a major cause of bacterial endocarditis. Despite the introduction of new semisynthetic antibiotics and surgical techniques, significant morbidity and mortality (5, 13, 15) still occur as a result of this disease, especially in the nonaddicted population (1). The overall mortality rate of patients with staphylococcal endocarditis treated with nafcillin, or its equivalent, is approximately 40% (13).

Approximately 80% of patients with *S. aureus* endocarditis are cured with clindamycin therapy (2); however, clinical experience is limited and confined almost exclusively to heroin addicts with tricuspid valve disease, for which there is a low mortality rate irrespective of the drug regimen (1, 2). Although clindamycin is active against *S. aureus* in vitro, its usefulness in treating endocarditis may be limited for several reasons: (i) it may be less bactericidal than the penicillins; (ii) resistant strains are encountered occasionally (10); (iii) resistance may develop during therapy in experimental animals (8) and in humans (12); and (iv) pseudomembranous colitis may develop. The latter reaction does not appear to be dose related and is less prominent when clindamycin is administered parenterally. The other obstacles listed might be eliminated with higher doses of clindamycin. Finally, the suitability of this agent for intramuscular administration gives it an important advantage over the semisynthetic penicillins or vancomycin in the therapy of heroin addicts, in whom superficial veins are often absent. These considerations led us to an evaluation of the therapeutic effectiveness of clindamycin and nafcillin against experimentally induced staphylococcal endocarditis in rabbits.

**MATERIALS AND METHODS**

**Test organism.** The *S. aureus* strain used in the in vivo studies was isolated from a patient with endocarditis. Its characteristics were described in an earlier study (7). The minimum inhibitory and bactericidal concentrations of clindamycin for this strain were identical (0.125 μg/ml); the corresponding concentrations of nafcillin were also identical (0.25 μg/ml).

**Production of endocarditis.** Experimental endocarditis was induced in New Zealand white rabbits (2 to 3 kg) by modifications of techniques described previously (7). The animals were anesthetized with pentobarbital sodium administered intravenously. A polyethylene catheter (PE-90; Clay Adams) was then inserted through the right carotid artery into the left ventricle, the aortic valve was traumatized for 15 min, and 10⁶ colony-forming units (CFU) of washed *S. aureus* in 1 ml of 0.9% NaCl were injected through the catheter. The catheter was then removed. All procedures were performed by the same operator to assure uniformity of technique. The inoculum was obtained from 24-h growth in Trypticase soy broth (BBL Microbiology Systems) at 37°C, verified by optical density readings of 0.113 on a Gilford spectrophotometer (model 2400), and diluted serially on Trypticase soy agar plates. Surgical mortality was ≤5%, and no wound infections occurred.

Endocarditis, which developed in 95% of the rabbits, was verified 24 h after inoculation by the pres-
ence of fever (≥39.6°C) and positive cultures of serially diluted venous blood (1.0 ml) on Trypticase soy agar pour plates.

**Experimental design.** Only those animals with positive blood cultures 24 h after inoculation were retained in the study because positive blood cultures correlate directly with the presence of endocarditis (7). Treatment with clindamycin or nafcillin was initiated at that time. Both drugs were administered intramuscularly every 8 h for 5 days, clindamycin at doses of 6.25, 12.5, 25.0, or 50.0 mg/kg and nafcillin at a dose of 200 mg/kg. On day 2 of therapy, serum was obtained and stored at −70°C for measurement of serum antibiotic levels and inhibitory and bactericidal titers. This period of storage (≤2 weeks) did not influence the assay results. Sixteen untreated animals served as controls.

All of the animals were killed 8 h after the last doses of antibiotic were given. The hearts were removed aseptically, and the aortic vegetations were excised and weighed (range, 0.05 to ≥0.4 g). After homogenization in the Teflon tissue grinder, the vegetations were diluted serially on Trypticase soy agar pour plates and incubated at 37°C for 24 h. Sterile vegetations were expressed as log_{10} 2.0 CFU/g, as the largest weight plated was ≈ 0.1 g, and the lower limit of sensitivity was approximately 100 CFU/g. The mean CFU per gram of vegetation were calculated for each group; data were compared with an unpaired Student’s t test.

**Antibiotic levels.** Serum concentrations of antibiotics were determined by two agar well diffusion techniques. Both assays had a reproducibility of ±10% and a lower limit of sensitivity of ±0.3 μg/ml.

**Serum inhibitory and bactericidal activity.** All serum inhibitory and bactericidal titers were determined by a microtiter technique with an inoculum of 10^5 CFU of the test strain in test serum diluted with normal pooled rabbit serum to 50% with Mueller-Hinton broth. The inhibitory titer was recorded as the highest dilution of serum that prevented visible turbidity after 24 h at 37°C; the bactericidal titer was considered the highest dilution that resulted in complete sterility upon subculture of 0.1 ml on Trypticase soy agar pour plates with further incubation (24 h at 37°C).

**RESULTS**

**Results of therapy.** At the higher doses, clindamycin was as effective as nafcillin in eradicating *S. aureus* from aortic valve vegetations. As shown in Table 1, there was a significant (P < 0.05) reduction in the mean numbers of *S. aureus* in aortic valve vegetations in all treated groups as compared with the controls. Although the vegetation titers were slightly higher in the two high-dose clindamycin groups than in the nafcillin group, these differences were not significant (P = 0.32 and 0.10 for the groups receiving 50 and 25 mg of clindamycin per kg, respectively). At lower doses, however, clindamycin did not eradicate the bacteria as well as did nafcillin (P = 0.007 and 0.003 for the groups receiving 12.5 and 6.25 mg of clindamycin per kg, respectively). Only the two higher doses of clindamycin produced results equivalent to those attained with nafcillin when the numbers of sterile valves (e.g., no growth under the conditions described) were compared. No resistant organisms were isolated postmortem, as determined by streaking onto Mueller-Hinton agar containing 0.5 μg of either antibiotic per ml.

**Serum antibiotic concentrations.** Peak serum levels of antibiotics were reached between 30 and

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**TABLE 1. Results of therapy of rabbits with experimental staphylococcal endocarditis**

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg intramuscularly every 8 h)</th>
<th>Vegetation titer (mean CFU/g ± SD)</th>
<th>No. of rabbits with sterile vegetations/total tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0</td>
<td>7.76 ± 2.31</td>
<td>0/16</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>50</td>
<td>2.67 ± 1.27</td>
<td>8/12</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>3.33 ± 1.98</td>
<td>6/10</td>
</tr>
<tr>
<td></td>
<td>12.5</td>
<td>4.36 ± 1.80</td>
<td>2/12</td>
</tr>
<tr>
<td></td>
<td>6.25</td>
<td>4.55 ± 2.20</td>
<td>1/13</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>200</td>
<td>2.31 ± 0.53</td>
<td>9/12</td>
</tr>
</tbody>
</table>

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FIG. 1. Mean serum drug concentration versus time after injection of rabbits with experimental staphylococcal endocarditis. Symbols: (●—●) nafcillin, 200 mg/kg; (●—○) clindamycin, 50 mg/kg; (○—○) clindamycin, 25 mg/kg; (▲—▲) clindamycin, 12.5 mg/kg; and (▲—▲) clindamycin, 6.25 mg/kg.
TABLE 2. Serum bactericidal titers in rabbits with experimental staphylococcal endocarditis treated with clindamycin or nafcillin

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>Serum bactericidal titer (range) at indicated time after dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5 h 1 h 2 h 4 h 6 h 8 h</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>6.25</td>
<td>1:16 1:16 1:8–1:16 1:2–1:8 1:4 1:2</td>
</tr>
<tr>
<td></td>
<td>25.0</td>
<td>1:32–1:128 1:32–1:64 1:32–1:64 1:32 1:8–1:32 1:8–1:32</td>
</tr>
<tr>
<td></td>
<td>50.0</td>
<td>1:64–1:256 1:64 1:64 1:32 1:32 1:32</td>
</tr>
</tbody>
</table>

60 min after administration and closely approximated those found in humans (Fig. 1). The serum concentration of nafcillin at 30 min was 49.5 μg/ml; this declined to 6.6 μg/ml by 8 h, with a serum beta half-life of 2.4 h. The peak concentrations of clindamycin were obtained at either 30 or 60 min and were 3.3, 4.3, 6.2, and 11.9 μg/ml for the 6.25-, 12.5-, 25-, and 50-mg/kg doses, respectively. Trough levels were between 0.3 and 2.8 μg/ml, depending on the dose used. The serum beta half-life for clindamycin was 3.7 h.

**Serum bactericidal activity.** Although there was some interanimal variation, the serum bactericidal titers closely correlated with the mean serum levels of the drug (Table 2). The serum bactericidal titers in rabbits treated with nafcillin were highest at 30 min (1:128 to 1:256) and were 1:16 in all animals just before administration of the next dose. The serum bactericidal titers observed with clindamycin were dose dependent and ranged from peak titers of 1:32 to 1:256 in the two high-dose groups to 1:16 to 1:32 in the low-dose groups (Table 2). Trough serum bactericidal titers were ≥1:8 only for the two high-dose groups.

**DISCUSSION**

This study showed that clindamycin at doses of 25 and 50 mg/kg is as effective as nafcillin at a dose of 200 mg/kg in the treatment of experimental staphylococcal endocarditis in rabbits. Optimal results were obtained when peak serum concentrations of clindamycin exceeded 6.2 μg/ml, levels achievable with standard parenteral doses in humans; resistance to clindamycin was not observed. It should be recognized that all experiments were done to assess the results of therapy for 5 days, an arbitrary endpoint. More prolonged therapy might well be more effective.

These studies clearly showed the dose dependence of clindamycin in the treatment of experimental staphylococcal endocarditis. Results equivalent to those attained with nafcillin were achieved with clindamycin only when peak serum concentrations of clindamycin exceeded 6.2 μg/ml. These levels are slightly higher than those obtained after intramuscular administration of 300 to 600 mg in normal volunteers (3). The best results were attained in our study when serum levels of clindamycin reached approximately 11 μg/ml; concentrations in this range require intravenous infusion of 600 to 900 mg in normal persons, but serum levels may need to be higher in infected patients (4). The doses usually used in treating endocarditis in humans (450 to 600 mg administered intramuscularly or intravenously every 6 h [2, 12]) may be suboptimal.

The relationship between the therapeutic results obtained with clindamycin and the serum bactericidal titers is interesting. For instance, 14 of 22 rabbits from rabbits receiving the two higher doses of clindamycin were culture negative (≤log_{10} 2.0 CFU/g) postmortem. In contrast, only three values from the 25 rabbits receiving the two lower doses of clindamycin were similarly negative (Table 1). Favorable results were obtained with those clindamycin regimens that produced trough serum bactericidal titers of ≥1:8 (Table 2). Because the dosage interval (8 h) was held constant for all the clindamycin regimens, it was not possible to discern the relative contribution to the therapeutic outcome of achieving a certain peak or trough serum bactericidal titer. However, the data do suggest that maintenance of an adequate serum bactericidal titer during most of the dosage interval may be more important than the actual serum bactericidal titer achieved. This concept has been emphasized recently (9). Comparable data on serum bactericidal titers during clindamycin therapy of endocarditis in humans are not available.

Clinical experience with clindamycin therapy of staphylococcal endocarditis is limited essentially to tricuspid valve disease in intravenous drug abusers (2, 12), in whom mortality is characteristically low (1). Our study examined aortic valve disease, which generally produces significant morbidity and mortality. The overall success rate of clindamycin therapy of staphylococcal endocarditis in humans is approximately...
ferences were seen between the effects of semisynthetic penicillin therapy and clindamycin therapy in staphylococcal endocarditis in a recent study (6); in several patients, clindamycin was substituted for cephalothin or vancomycin because of intolerance to either of the latter agents (6). Intravenous clindamycin followed by oral clindamycin was curative in several patients (6). It is possible that therapeutic success could be improved by clindamycin-aminoglycoside combinations because these agents are often synergistic in vitro (14). In addition, other actions of clindamycin may be important in treating endocarditis. These may include an alteration in bacterial virulence factors at subinhibitory concentrations (G. C. Gemmell and M. K. A. Amir, Abstr. Int. Symp. Streptococci Streptococcal Dis. 7th, Oxford, United Kingdom, abstr. no. 26, 1978), increased phagocytosis of clindamycin-exposed bacteria by leukocytes or increased clindamycin concentrations within phagocytes (W. L. Hand, N. K. Thompson, and J. D. Johnson, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 725, 1980; M. S. Klemper, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 727, 1980), or alterations in bacterial adherence to host surfaces (11).

Our experiments showed that clindamycin (at appropriate serum concentrations and serum bactericidal titer) is as effective as nafcillin in the treatment of experimental staphylococcal endocarditis. Clindamycin should not be considered the drug of choice for this disease, primarily because it has a slow bactericidal activity as compared with penicillins or cephalosporins (8, 14). Although clindamycin may be effective at full parenteral doses in the treatment of S. aureus endocarditis, it should be reserved for situations in which antistaphylococcal penicillins, cephalothin, cefazolin, or vancomycin have either failed or are poorly tolerated.

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LITERATURE CITED