Short-Term Intramuscular Therapy with Procaine Penicillin Plus Streptomycin for Infective Endocarditis due to Viridans Streptococci

WALTER R. WILSON, M.D., JOSEPH E. GERACI, M.D., CONRAD J. WILKOWSKE, M.D., AND JOHN A. WASHINGTON II, M.D.

SUMMARY Thirty-three patients with viridans streptococcal infective endocarditis were treated for two weeks with intramuscular procaine penicillin, 1.2 million units every 6 hours, plus streptomycin, 500 mg intramuscularly every 12 hours. Nine patients (27%) had infections with relatively penicillin-resistant microorganisms (MIC > 0.1 μg/ml or MBC ≥ 3.12 μg/ml). Follow-up ranged from 2 months to 3.5 years. There were no relapses. Mild vestibular toxicity developed in one patient. One patient died two months after completion of antimicrobial therapy from sudden onset of severe congestive heart failure. Seven patients required cardiac valve replacement after completion of antimicrobial therapy. None died. We believe that this therapeutic regimen is effective antimicrobial therapy for infective endocarditis caused by viridans streptococci, irrespective of in vitro microbiologic data.

STREPTOCOCCI OF THE VIRIDANS GROUP are reported to be the most common bacterial etiologic agents of infective endocarditis, constituting about 30 to 40% of cases. Penicillin alone or in combination with streptomycin is the preferred antimicrobial therapy for these patients. The use of short-term combined penicillin-streptomycin therapy for infective endocarditis caused by penicillin-sensitive streptococci was first suggested more than 25 years ago, but it has not gained wide acceptance.

In a prospective study, we treated 33 patients who had infective endocarditis caused by viridans streptococci for two weeks with intramuscular procaine penicillin plus streptomycin. Our experience with these patients is the subject of this report.

Material and Methods

Only patients with infective endocarditis caused by streptococci of the viridans group were enrolled in our prospective study. Our criteria for the diagnosis of infective endocarditis were (1) at least two positive blood cultures with viridans streptococci on at least two separate days and (2) at least two of the following clinical signs — fever, development of a new regurgitant murmur, newly developed splenomegaly, or peripheral embolic phenomenon.

Congestive heart failure was categorized according to criteria defined by the New York Heart Association. Antimicrobial susceptibility tests were done by methods described elsewhere. Minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) were determined by serial dilution in broth in concentrations ranging from 100 to 0.09 μg/ml, and the results were expressed as the lowest concentration of antibiotic that killed at least 99.9% of the initial inoculum. Serum bactericidal tests (SBT) were determined during the third day of treatment on a serum sample taken one hour after intramuscular injection of procaine penicillin and streptomycin; the results were expressed as the greatest dilution of serum that killed at least 99.9% of the inoculum.

Relative penicillin resistance of viridans streptococci was defined as MIC > 0.1 μg/ml or MBC ≥ 3.12 μg/ml, as measured by broth dilution. Antimicrobial therapy in each patient was procaine penicillin G, 1.2 million units every 6 hours, and streptomycin, 500 mg every 12 hours, given intramuscularly for 14 days. The 12-hourly injections of procaine penicillin and streptomycin were administered simultaneously.


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Relapse of infection was defined as signs and symptoms of infective endocarditis with positive blood cultures for viridans streptococci occurring within 2 months from the time of completion of antimicrobial therapy.

Follow-up ranged from 2 months to 3.5 years. Blood cultures were obtained in all patients at 1- and 2-month post-treatment intervals.

**Results**

From January 1972 through December 1975, infective endocarditis caused by viridans streptococci developed in 53 patients. Of these 53 patients, 20 (38%) were excluded from our protocol — in six of these patients, treatment was initiated with other antimicrobial agents before the diagnosis of infective endocarditis was established or before the patient was enrolled in the protocol; seven patients had a history of penicillin allergy; four had prosthetic valve endocarditis; two had marked thrombocytopenia and severe heart failure with presumed poor peripheral perfusion; and one patient left the hospital against medical advice before therapy could be completed. The remaining 33 patients (62%) were enrolled in this study.

Of these 33 patients, 22 (67%) were males and 11 (33%) were females. The mean age was 58.4 years (range 14 to 78 years). The mitral valve alone was involved in 24 patients (73%), the aortic valve alone in seven (21%), and the aortic and mitral valves in two (6%). All patients with mitral valve infection had regurgitant murmur; six of nine patients with aortic infection had regurgitant murmur.

MIC values were $\leq 0.09$ µg/ml in 25 cases (76%); 0.19 µg/ml in two cases (6%); and indeterminate in six cases (18%) (table 1). MIC could not be determined by broth dilution in these six cases because no growth was visible in the control or in any of the tubes containing dilutions of penicillin. Also, in these six cases (and in the remaining 27), MIC values were measured by agar dilution:10 MIC was $\leq 0.1$ µg/ml in four and 0.5 µg/ml in two cases. In the remaining 27 cases MIC by agar dilution was $\leq 0.1$ µg/ml in 26 and 0.5 µg/ml in one.

MBC values were $< 3.12$ µg/ml in 23 cases (70%) and indeterminate in two (6%). The isolates from these latter two cases exhibited poor growth in the control tubes not containing penicillin. Since growth of these two strains in the control tubes was inadequate, MBC values were considered inaccurate. SBT results were $\leq 1:8$ in 30 cases (91%). Of those cases with MBC $\geq 3.12$ µg/ml, only one had an SBT value $< 1:8$ (1:4). The streptococci from the remaining three patients (9%) with SBT $< 1:8$ each had an MIC of $\leq 0.09$ µg/ml and an MBC of 0.19 µg/ml. SBT values in these three cases were 1:4.

In table 2, cases are distributed according to the class of congestive heart failure present at the initiation of antimicrobial therapy. Seven patients (21%) underwent cardiac valve replacement at various intervals after completion of antimicrobial therapy. All of these seven had evidence of previous infective endocarditis at the time of surgery, but gram-stained smears and cultures of the excised valves were negative in each case. None of the 24 patients with Class I or Class II congestive heart failure required cardiac valve replacement.

Mild vestibular toxicity occurred in one patient, a 78-year-old man with renal insufficiency. None of the remaining 32 patients had evidence of toxicity from antimicrobial therapy. The intramuscular injections were well tolerated.

Of the 33 patients in our study, one died. This patient died elsewhere about three weeks after completing antimicrobial therapy. In vitro microbiologic studies of the isolate from this patient were MIC $\leq 0.09$ µg/ml, MBC 3.12 µg/ml, and SBT 1:8. This patient had infective endocarditis involving the mitral valve and Class III congestive heart failure. Cardiac valve replacement was suggested to her; however, she elected to return home without surgery. When she returned home, the congestive heart failure abruptly worsened and she died two days later. Antemortem blood cultures were reportedly negative. Postmortem examination performed elsewhere did not reveal evidence of active infective endocarditis; postmortem cultures of the previously infected mitral valve were reportedly negative.

Follow-up of the remaining 32 patients ranged from 2 months to 3.5 years. Blood cultures were negative at 1- and 2-month intervals after completion of antimicrobial therapy in these 32 patients, none of whom had clinical or laboratory signs of relapse of infective endocarditis.

**Discussion**

Hunter12 originally suggested the use of short-term, combined penicillin-streptomycin treatment for patients with infective endocarditis caused by viridans streptococci. The rationale for this therapy was based on in vitro studies demonstrating synergy between penicillin and streptomycin against several isolates of viridans streptococci from patients with infective endocarditis. Recent studies have demonstrated conclusively that penicillin and streptomycin act synergistically against viridans streptococci.10-17

In early reports, one of us (J.E.G.) reported only one

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**Table 1. Relatively Penicillin-Resistant Isolates of Viridans Streptococci**

<table>
<thead>
<tr>
<th>MIC (µg/ml)</th>
<th>MBC (µg/ml)</th>
<th>SBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 0.09$</td>
<td>3.12</td>
<td>1:256</td>
</tr>
<tr>
<td>$\leq 0.09$</td>
<td>3.12</td>
<td>1:8</td>
</tr>
<tr>
<td>$\leq 0.09$</td>
<td>12.5</td>
<td>1:128</td>
</tr>
<tr>
<td>$\leq 0.09$</td>
<td>12.5</td>
<td>1:4</td>
</tr>
<tr>
<td>$\leq 0.09$</td>
<td>12.5</td>
<td>1:128</td>
</tr>
<tr>
<td>$\leq 0.19$</td>
<td>25</td>
<td>1:8</td>
</tr>
<tr>
<td>$\leq 0.09$</td>
<td>100</td>
<td>1:32</td>
</tr>
<tr>
<td>$\leq 0.19$</td>
<td>1.56</td>
<td>1:32</td>
</tr>
<tr>
<td>$\leq 0.09$</td>
<td>25</td>
<td>1:64</td>
</tr>
</tbody>
</table>

Abbreviations: MIC = maximum inhibitory concentrations; MBC = minimum bactericidal concentrations; SBT = serum bactericidal tests.

**Table 2. Class of Congestive Heart Failure and Valve Replacement**

<table>
<thead>
<tr>
<th>Class of CHF</th>
<th>Patients</th>
<th>Valve replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>(%)</td>
</tr>
<tr>
<td>0</td>
<td>10 (30)</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>6 (18)</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>8 (24)</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>6 (18)</td>
<td>4 (66)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (9)</td>
<td>3 (100)</td>
</tr>
</tbody>
</table>

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relapse among 66 surviving patients treated for two weeks with varying doses of intramuscular penicillin and streptomycin and recommended short-term combined penicillin-streptomycin as conventional therapy. Together with our 33 patients, these additional 66 patients constitute a total of 99 patients treated similarly with only one relapse. Other studies reported relapse rates from 6 to 11% in patients with infective endocarditis caused by viridans streptococci treated with combined penicillin-streptomycin therapy. These relapse rates are lower than those reported for patients treated with penicillin alone for two weeks (15 to 17%).19, 20 and slightly exceed those reported from early studies of patients treated with penicillin alone for four weeks (5%).21, 22 In two recent retrospective studies (Karchmer AW: personal communication), no relapses occurred among patients treated for 4 or more weeks with parental penicillin alone. Wolfe and Johnson16 found no relapses in a retrospective study of 35 patients with infective endocarditis caused by penicillin-susceptible viridans streptococci (MIC 0.1 \( \mu \text{g/ml} \)) who were treated with a mean daily dose of 11.4 million units of penicillin for 30.4 days and 1.2 g of streptomycin for 13.4 days.

That the combination of penicillin and streptomycin is superior to penicillin alone in the treatment of these infections is supported by data obtained from studies of experimental animal endocarditis. Combined penicillin and streptomycin were more effective than penicillin alone in preventing experimental endocarditis27, 28 and in treating established infections.29, 30

In our prospective study, no relapses occurred among 33 patients treated for two weeks with intramuscular procaine penicillin and streptomycin. We are unaware of data comparing cure rates in patients with infective endocarditis caused by relatively penicillin-resistant strains of viridans streptococci. Some investigators suggest that when MIC values for viridans streptococci exceed 0.1 \( \mu \text{g/ml} \), patients should receive antimicrobial therapy identical to that for enterococcal endocarditis. According to our criteria for relative penicillin resistance, nine of our 33 patients (27%) had infections with relatively penicillin-resistant microorganisms. Our data suggest that antimicrobial therapy in these patients need not differ from that of patients with penicillin-susceptible isolates. The in vitro susceptibility data of viridans streptococci are somewhat difficult to interpret because they are a heterogeneous group of bacteria which comprise at least six species with varying growth characteristics and CO₂ requirements. Methods for testing their antimicrobial susceptibility are not standardized, and therefore, susceptibility data vary among laboratories. Moreover, in vitro susceptibility data may reflect interspecies differences and as yet incompletely studied intraspecies differences. In our experience, however, relative penicillin resistance did not affect mortality or relapse rates.

The low vestibular toxicity rate observed in our patients is similar to that reported by Tomssett and Hurst.11 Vestibular toxicity is more likely to occur in the elderly, in the presence of renal insufficiency, or with pre-existing vestibular dysfunction. We suggest that pretreatment audiograms and caloric determinations be obtained, and if signs of vestibular toxicity develop, or if pre-existing vestibular toxicity worsens, that streptomycin be discontinued. In patients who have renal insufficiency, we suggest that the dose of streptomycin be reduced and the streptomycin concentrations be monitored closely. Optimal serum concentration is estimated to be \( \leq 30 \mu \text{g/ml} \). Alternatively, patients who have renal insufficiency or pre-existing vestibular toxicity may be treated with 20 million units of intravenous penicillin alone, daily for 4 weeks. In these patients, the dose of penicillin may have to be adjusted according to the degree of renal insufficiency.

The mortality rate among our patients was low — 3%. The single death resulted from sudden, severe worsening of pre-existing Class III congestive heart failure. In patients with severe congestive heart failure caused by infective endocarditis, cardiac valve replacement may be indicated.29 The seven patients in our series who required cardiac valve replacement had Class III or IV congestive heart failure complicating the infective endocarditis. The operative risk of cardiac valve replacement in these patients appears to be related not to the presence of infective endocarditis but rather to the degree of congestive heart failure present at the time of surgery.30

Based on our data, we believe that intramuscular procaine penicillin, 1.2 million units every 6 hours, and streptomycin, 500 mg every 12 hours, daily for 2 weeks is effective antimicrobial therapy for infective endocarditis due to viridans streptococci in non-thrombocytopenic patients with adequate peripheral perfusion. This therapy appears to be efficacious irrespective of the MIC and MBC susceptibility data and appears to be at least as effective as treatment with penicillin alone for 4 weeks or combined penicillin and streptomycin therapy for 2 weeks followed by penicillin alone for an additional two weeks. The risk of vestibular toxicity associated with streptomycin use is small. The advantages of treatment for two weeks with intramuscular antimicrobials over treatment for four weeks with intravenous antimicrobials are clear — shortened hospitalization period with reduced cost to patients, more efficient use of hospital personnel and facilities, and avoidance of potential hazardous complications associated with the use of intravenous therapy. In our opinion a burden rests on those who advocate four weeks of therapy to demonstrate that this longer duration of treatment is more effective, or less toxic, or more cost-effective than short-term therapy.

References
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Impairment of Antipyrine Clearance in Humans by Propranolol

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SUMMARY The effect of propranolol on antipyrine clearance in humans was evaluated in six healthy volunteers who received single 1.4 to 1.5 g doses of intravenous antipyrene on two occasions. The first (control) antipyrene trial was without concurrent drug administration; the second trial was done during treatment with therapeutic doses of propranolol (40 mg every 4 to 6 hours). Antipyrene elimination half-life ($t_{1/2}$), volume of distribution ($V_d$), and total clearance were determined after each trial. In all subjects iso-proterenol sensitivity decreased markedly during propranolol treatment, indicating a high degree of beta blockade produced by the drug. Mean antipyrene $t_{1/2}$ during the propranolol treatment period was significantly prolonged, and total clearance significantly reduced, over the control values. Twenty-four-hour urinary excretion of 4-hydroxyantipyrene, the major metabolite of antipyrene, likewise was reduced from 23.6% of the dose on the control trial to 14.8% of the dose during propranolol coadministration ($0.1 < P < 0.2$). $V_d$ however, was nearly identical during both trials (0.62 L/kg). Thus propranolol prolongs the half-life and reduces the clearance or biortransformation rate of antipyrene, a drug whose clearance is independent of hepatic blood flow. Propranolol may influence the activity of hepatic microsomal enzymes responsible for drug hydroxylation.

PROPRANOLOL IS CURRENTLY APPROVED for clinical use in the treatment of cardiac arrhythmias, angina pectoris, and hypertension. In these settings it is commonly coadministered with other pharmacologic agents, but there is little information available on possible pharmacokinetic interactions of propranolol with other drugs used to treat these disease states. Such interactions could be of considerable clinical importance if they lead to decreased efficacy or enhanced toxicity of other coadministered drugs. The present study assessed the interaction of propranolol with antipyrene, a compound that shares with many other drugs a primary biortransformation pathway involving hydroxylation by the liver. As such, the pharmacokinetic profile of antipyrene is extensively used as an index of drug-metabolizing capacity in humans, and appears to be sensitive to factors that stimulate or inhibit drug metabolism.
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