

STREPTOMYCIN FOR PENICILLIN-RESISTANT SUBACUTE BACTERIAL ENDOCARDITIS

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ALTHOUGH penicillin is the drug of choice for the treatment of subacute bacterial endocarditis due to nonhemolytic streptococci, there is a group of cases in which the antibiotic agent fails to arrest the infection. In some of these cases the organism is resistant to penicillin from the beginning, while in others resistance apparently is acquired during the course of therapy. Treatment, in the former instances, does not affect the fever or the clinical course of the illness, but in cases belonging to the latter group, the evidence of infection is temporarily controlled, only to relapse while the drug is still being administered or shortly after it has been discontinued. Hunter¹ has recommended that streptomycin be employed in the treatment of these penicillin-resistant cases, and the present report summarizes two instances in which therapy of this kind successfully controlled the infection.

Case Reports

Case 1. A white man, aged 42, had had several teeth removed two and one-half months before his first visit to the Clinic. Approximately twelve hours after the extractions he experienced a severe chill followed by fever. Six weeks later, because of increasing weakness and fatigue, persistent afternoon fever, and frequent night sweats, he was admitted to a hospital. A blood culture yielded a growth of *Streptococcus viridans*, and an unknown amount of penicillin was administered by intramuscular injection every three hours for three and one-half days. He was then discharged, but the fever and other symptoms returned within two or three days. Three weeks later he was admitted to the Clinic. There was a history of rheumatic fever in childhood.

On physical examination, the temperature was 100.4 F., the pulse rate 120, and the blood pressure 108 systolic, 68 diastolic. The heart was not enlarged, and its rhythm was regular. A moderate systolic murmur was present at the apex. The spleen was readily palpable. There were no petechiae. The blood culture was positive for *Str. viridans*.

Penicillin was administered in doses of 25,000 units every two hours by intramuscular injection. The temperature returned to normal within twenty-four hours and did not rise above normal during the remaining seven days of hospitalization. Penicillin was continued at home in the same amounts for the next two weeks, but at the end of that time the temperature again became elevated and the patient therefore was readmitted to the hospital. The blood culture was positive for *Str. viridans*. The dosage of penicillin was increased to 50,000 units every two hours. The temperature returned to normal on the fourth day, but when treatment was terminated at the end of six weeks, fever reappeared almost immediately, and the patient experienced several mild chills. A blood culture made three days after the last injection of penicillin again yielded a growth of *Str. viridans*. Penicillin was resumed in doses of 50,000 units every two hours, and intramuscular injections of streptomycin also were given in doses of 0.5 Gm. every three hours until a total of 20 Gm. had been administered. The fever was promptly controlled. Penicillin was continued for three and one-half weeks. It is now fourteen months since treatment was completed, and during this time there has

been no evidence of relapse. Periodic blood cultures have been uniformly negative, and for several months the patient has been doing light work.

Case 2. A white woman, aged 45, had had daily low-grade fever for one year before coming to the Clinic and had noted gradually increasing general malaise, fatigue, weakness, and dyspnea on exertion. For many months she had received penicillin by intramuscular injection in amounts sufficient to give a daily total of 500,000 units to 1,000,000 units. Approximately 200,000,000 units of penicillin had been administered during this time, but the fever and other symptoms had not been noticeably affected. There was a history of growing pains in childhood.

At the time of admission, the temperature was 103.2 F., the pulse rate 120 per minute, and the blood pressure 134 systolic, 40 diastolic. The skin and mucous membranes were pale, a "splinter hemorrhage" was present beneath the nail of the left third finger, and there was a small petechia in the conjunctiva of the left lower eyelid. The heart was moderately enlarged, and its rhythm was regular. A short systolic murmur was present at the aortic area, and the aortic second sound was followed by a prolonged, low-pitched diastolic murmur which was transmitted downward along the left border of the sternum. A soft systolic murmur was present at the apex. The left ankle was swollen and moderately tender. Blood cultures were positive for *Str. viridans*.

Penicillin by intramuscular injection in doses of 50,000 units every two hours had no effect upon the fever, and at the end of five days the dose was increased to 100,000 units every two hours. The temperature remained elevated, and at the end of twelve days' treatment the blood culture was still positive for *Str. viridans*. Penicillin therapy was continued, but the patient was also placed upon streptomycin in doses of 0.5 Gm. by intramuscular injection every three hours. The temperature returned to normal within forty-eight hours, but on the following day fever again developed and was accompanied by a generalized macular rash, pharyngitis, and vertigo. Streptomycin was continued until a total of 30 Gm. had been administered. The temperature remained elevated throughout this period, reaching a maximum of 104 F. on the sixth day, but returned to normal within twenty-four hours after the last dose and remained normal during the remaining four weeks of hospitalization. Penicillin was continued until the day of discharge. There has been no recurrence of symptoms, and the patient is in satisfactory health one year after leaving the hospital.

Discussion

The 2 cases which have been presented demonstrate that under certain circumstances streptomycin may be of life-saving importance in the treatment of subacute bacterial endocarditis. Because of the frequency with which its use in large amounts results in symptoms of toxicity, the drug, however, is not to be preferred to penicillin in the management of the usual case of this condition. Penicillin in adequate amounts can be expected to result in the cure of at least 75 per cent of all cases of nonhemolytic streptococcus endocarditis, and because the incidence of undesirable reactions to this antibiotic agent is so remarkably low, it is the preparation of choice. It is believed that streptomycin should be used only in those cases in which penicillin fails to control the infection. The recent introduction of caronamide as an agent for enhancing penicillin serum concentrations^{2,3} offers a promising prospect of considerably reducing the number of cases of subacute bacterial endocarditis in which penicillin therapy is unsuccessful. As a result the role of streptomycin in the treatment of this condition probably will be limited further, but occasional cases in which the use of the drug will be indicated undoubtedly will still occur.

Measurements of the penicillin sensitivity of the infecting organism are desirable in all cases of subacute bacterial endocarditis, but the results of such

measurements cannot be taken as an infallible guide to treatment and prognosis.⁴ In the first of the cases reported in the present communication, growth of the organism was inhibited by penicillin in a concentration of 0.03 units per cc., while in the second, 0.25 units per cc. were required. These findings suggest that larger amounts of penicillin might have been effective, although theoretically the dosage employed in the latter part of the treatment of the first patient should have been sufficient.

Since these patients were treated it has become our practice to administer penicillin by continuous intramuscular drip rather than by intermittent intramuscular injection and to begin treatment with a dose of 1,000,000 units a day. As soon as the penicillin sensitivity of the infecting organism has been determined, the daily amount of the drug is adjusted up or down to the smallest amount that will maintain a serum level approximately four times as high as the amount required to inhibit the growth of the organism *in vitro*. Dawson and Hunter⁵ have recommended this level and have published a table which can be used as a guide to the dose of penicillin necessary to obtain the desired serum concentration when continuous intramuscular administration is employed. This method is very satisfactory when the indicated daily dose is 2,000,000 units or less, but for larger amounts continuous intravenous drip is to be preferred. Treatment is continued for three weeks, and the patient is then kept under close observation for several weeks for evidence of relapse.

In the cases presented, penicillin was continued during the time streptomycin was being administered. Whether the successful results were due to the combined use of the two preparations or are to be attributed to streptomycin alone cannot be stated. Hunter,¹ however, has pointed out certain considerations which might make combined antibiotic therapy more effective than the use of either penicillin or streptomycin alone.

Summary

Two cases of subacute bacterial endocarditis due to *Str. viridans* are reported in which penicillin failed to control the infection but recovery resulted when streptomycin was added to the treatment.

References

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