SUBACUTE BACTERIAL ENDOCARDITIS TREATED UNSUCCESSFULLY WITH SULFAPYRIDINE

A Report of Five Cases

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Recent medical literature has contained a few reports of the successful treatment of subacute bacterial endocarditis with sulfanilamide or sulfapyridine. The most encouraging of these have been the reports of Kelson and White[1] and of Major[2]. Recovery occurred in three of seven cases treated by Kelson and White with sulfapyridine and heparin in combination and in three of seven cases treated by Major with sulfanilamide or sulfapyridine alone. Stimulated by these reports, we have employed sulfapyridine in the treatment of five patients with subacute bacterial endocarditis, but the results have been uniformly disappointing. Two patients have died and the others are unimproved. Streptococcus viridans was the responsible organism in two of the cases, while a nonhemolytic streptococcus was found in two others, and in the fifth case an anaerobic streptococcus was recovered.

CASE REPORTS

Case 1: A white boy, eighteen years of age, was admitted to the hospital on November 1, 1939 because of chills, fever, and sweats, one week in duration. The onset of symptoms had been sudden and there had been no recent acute illness. The past medical history disclosed nothing suggestive of an earlier rheumatic infection.

Physical examination revealed a well-nourished individual who did not appear particularly ill. The temperature, however, was 104° F. and the pulse rate 140 per minute. The blood pressure was 148 mm. systolic and 0 diastolic. The heart was not enlarged and its rhythm was regular. A prolonged diastolic murmur was present over the aortic area and was transmitted down along the left sternal border and to the apex. A small splinter hemorrhage was found in the nail bed of one finger and another small petechia was present on another finger. The spleen and liver were not palpable. Blood cultures taken on the first and second hospital days yielded growths of streptococcus viridans within 48 hours. A diagnosis of rheumatic heart disease with aortic insufficiency and subacute bacterial endocarditis was made.

Sulfapyridine was started on the third hospital day. Seven grams of the drug were administered during the first twenty-four hours and 6 grams were given every twenty-four hours thereafter. This dosage maintained a sulfapyridine level in the blood of 4.5 mg. to 5.0 mg. per 100 cc. The temperature fell to normal within twenty-four hours and remained normal until the time of discharge on the ninth hospital day. A blood culture taken on the day of discharge remained sterile.

Sulfapyridine was continued in doses of 1 gram every four hours day and night, under the supervision of the patient's physician. Except for a transient rise to 102° F. a few days after returning home, the temperature remained normal. Three blood cultures taken three weeks later remained sterile. The dosage of sulfapyridine was then reduced to 1 gram every six hours. Two weeks later the

temperature again started rising to 100° to 100.5° F. every afternoon. Blood cultures taken on December 30 were again positive for streptococcus viridans. The patient was instructed to continue with his medication although it was felt that a sufficient amount had been given for an adequate therapeutic trial.

Case 2: A white woman, aged twenty-nine years, was admitted to the hospital on October 31, 1939 because of severe frontal headache, nausea, vomiting, chills, and fever. Thirteen teeth had been extracted one month earlier and the symptoms had developed one week after this. The patient had had rheumatic fever as a child.

Physical examination revealed slight enlargement of the heart to the left and a loud systolic murmur at the apex. The liver and spleen were not palpable and no petechiae were present. During the first two days in the hospital, the temperature rose to 102° F. and there was frequent vomiting. Blood cultures were taken and gave a growth of non-hemolytic streptococci within twenty-four hours. A diagnosis of rheumatic heart disease with mitral insufficiency and subacute bacterial endocarditis was made.

The patient was started on sulfapyridine in doses of 1 gram every four hours on the first day and 1 gram every six hours for thirty-two days thereafter. The blood sulfapyridine level varied from 1.9 mg. to 3.6 mg. per 100 cc. The temperature fell to normal within twelve hours after the first dose of the drug and remained normal until the tenth hospital day. Following this there was a gradual return of fever to between 100° and 100.4° F. every afternoon, and this continued until the patient's discharge on December 2, 1939. Blood cultures on the day of discharge were still positive for non-hemolytic streptococci.

There was no decrease in the erythrocyte or leukocyte count or in the hemoglobin level during the period of sulfapyridine therapy. No petechiae or other evidence of embolic phenomena were observed at any time. The urine contained blood on one occasion but this, of course, may have been due to the passage of acetyl sulfapyridine crystals.

Case 3: A white man, thirty-six years of age and known to have central nervous system lues and luetic aortitis with aortic insufficiency, was admitted to the hospital on October 24, 1939. Eleven days earlier severe pain had developed suddenly in the lower back and five days later pain also had developed in the calf of the left leg. The pain in both regions persisted and was still present at the time of admission to the hospital. The patient also reported that for about three months he had been having frequent night sweats.

At the time of admission to the hospital the temperature was 100.6° F., the pulse rate 120 per minute, and the blood pressure 160 mm. systolic and 30 mm. diastolic. The heart was not enlarged and its rhythm was regular. A short systolic murmur was heard at the aortic area and the second sound was followed by a long diastolic murmur. There was a moderate apical systolic murmur. The spleen was palpable two finger breadths below the costal margin. There was no tenderness over the lower spine but movements of the lower back were extremely painful. The calf of the left leg was very tender. No petechiae were seen. The erythrocyte count was 3,970,000 per cu. mm. and the hemoglobin content 65 per cent. The white blood cell count was 6,600 per cu. mm. Blood cultures taken on three successive days yielded a non-hemolytic streptococcus. A diagnosis of luetic aortic insufficiency and subacute bacterial endocarditis was made.

The patient was started on sulfapyridine in doses of 1 gram every four hours day and night, and this maintained a blood sulfapyridine level of 10.6 mg. to 15.0 mg. per 100 cc. The temperature fell to normal within twenty-four hours of the first dose of the drug, and the pain in the back and leg promptly improved.

The temperature remained normal for nine days but two blood cultures taken during this time gave growths of non-hemolytic streptococci. Fever returned after the ninth day and the temperature eventually rose to as high as 105.6° F. Petechiae appeared in the fingers and conjunctivae, and there were repeated emboli to the kidneys, spleen, and central nervous system. After twenty-one days of sulfapyridine therapy, the leukocyte count began to decrease and, in spite of discontinuance of the drug, fell to 450 cells per cu. mm. with complete disappearance of the granulocytes. Repeated blood transfusions were of no benefit. The patient became comatose and expired on the thirty-eighth day in the hospital. Blood cultures made six days before death were still positive. Necropsy revealed aneurysmal dilatation of the proximal portion of the aorta and luetic involvement of the aortic valves with heavy vegetations on the valve cusps.

Case 4: A negro, aged fifteen years, entered the hospital on October 16, 1939 complaining of pain in the right hip. He stated that for several months he had felt generally under par and that a gradually increasing pallor of his lips had been noted. Two months before admission, the ankles had become swollen and painful and from this time on there had been a low grade afternoon fever. One month before entering the hospital, sudden severe pain had developed in the right hip, and a few days later similar pain had developed in the left hip. There was no past history of rheumatic infection.

Physical examination showed an obviously ill individual. The temperature was 100.4° F., the pulse rate 120 beats per minute, and the blood pressure 120 mm. systolic and 60 mm. diastolic. The heart was not enlarged and its rhythm was regular. At the apex a rumbling presystolic murmur was heard and the first sound was greatly accentuated. A long diastolic murmur was present at the aortic area and was transmitted down along the left sternal border. The liver and spleen were not palpable. There was marked clubbing of the fingers and toes. No petechiae were present. Movements of the right hip joint were quite painful.

The erythrocyte count was 3,380,000 per cu.mm. and the hemoglobin content 55 per cent. The white blood cell count was 11,300 per cu.mm. Blood cultures taken on four successive days yielded a streptococcus after incubation for five to seven days. Repeated attempts at identification of this organism by plating on blood agar were unsuccessful. A diagnosis of rheumatic heart disease with mitral stenosis and aortic insufficiency and subacute bacterial endocarditis was made.

The patient was started on sulfapyridine by mouth in doses of 1 gram every four hours day and night. The sulfapyridine concentration in the blood ranged from 2.8 mg. to 6.0 mg. per 100 cc. Because of severe nausea and vomiting, an attempt was made to administer the same dosage rectally but the blood sulfapyridine level fell to 1.3 mg. per 100 cc. The rectal administration of sodium sulfapyridine met with no more success. Sodium sulfapyridine was then administered intravenously in 5 per cent solution in amounts varying from 1.5 gm. to 6 gm. daily given in divided doses. During this period the sulfapyridine concentration in the blood ranged from 6.0 to 11.4 mg. per 100 cc. On the fifteenth day of treatment, and after the patient had received 70 gm. of sulfapyridine, the leukocyte count was 6,900 per cu.mm. After twenty-one days and 104.5 gm. of sulfapyridine, the white count had fallen to 1,950 per cu.mm. The drug was discontinued and the leukocyte count immediately began to rise. At no time during the course of treatment was the patient's temperature restored to normal. Blood cultures continued to yield an anaerobic streptococcus. There were repeated emboli to

the fingers, extremities, spleen, and kidneys. Death occurred on November 24, 1939, thirty-nine days after admission to the hospital.

Case 5: A white woman, thirty-four years of age, was admitted to the hospital on December 13, 1939 because of fever, weakness, loss of weight, and palpitation, four months in duration. She had been treated with sulfanilamide (80 gr. daily) for two weeks without benefit. No history of rheumatic infections could be obtained.

On examination the heart was not enlarged and its rhythm was regular. A moderate apical systolic murmur was present. The spleen was palpable at the costal margin. No petechiae were found. The erythrocyte count was 3,760,000 per cu.mm. and the hemoglobin content 58 per cent. The white blood cell count was 5000 per cu.mm. The urine contained a trace of albumin and a few red blood cells. Blood cultures gave a growth of streptococcus viridans in seventy-two hours.

During the first three days in the hospital, the maximum temperature ranged from 101.3° F. to 103.4° F. Numerous petechiae appeared in the finger tips and under the nails. On one occasion the patient complained of sudden severe pain in the left upper quadrant of the abdomen which was interpreted as due to embolism of the spleen. Sulfapyridine was started on the third day in doses of 1 gram every four hours day and night. The temperature fell to normal within twenty-four hours. The sulfapyridine blood level quickly rose to 14.9 mg. per 100 cc. and then fell to 5.6 mg. per 100 cc. when the dosage of the drug was reduced to 1 gram every six hours. Five days after starting therapy, the patient was discharged to carry on treatment under the supervision of her own physician. Fever returned, the temperature rising to 102° to 103° F. every afternoon. On January 19, 1940, after thirty-three days of sulfapyridine therapy, blood cultures were still positive for a green producing streptococcus. The sulfapyridine blood level was 5.9 mg. per 100 cc. and the drug was discontinued.

Summary

Sulfapyridine was employed unsuccessfully in the treatment of five cases of subacute bacterial endocarditis. The causative organism was streptococcus viridans in two cases, non-hemolytic streptococci in two cases, and an anaerobic streptococcus in the other. The dosage of sulfapyridine was adequate in every case according to generally accepted standards. The duration of treatment to date has varied from nineteen to fifty-seven days. Two of the patients have died. In the other three, the blood cultures have remained positive and the disease is following its usual progressive course.

1. Kelson, S. R. and White, P. D.: A new method of treatment of subacute bacterial endocarditis using sulfapyridine and heparin in combination; preliminary report, J. A. M. A. 113:1700-1702, (November 4) 1939.
2. Major, R. H.: Effect of sulfanilamide compounds on endocarditis, Am. J. M. Sc. (In press).