Sodium Gентisate in the Treatment of Acute Rheumatic Fever

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Five patients with acute rheumatic fever were treated with gentisate, the biologic oxidation product of salicylate. The clinical course of this group was contrasted with that of five patients who received salicylate. It was found that, in the doses employed, gentisate had an effect on the symptoms of acute rheumatic fever equal to that of salicylate, but that it produced none of the toxic reactions which were commonly found after salicylate administration. An oral dose of 2.0 Gm. of gentisate, every three hours, continued for at least ten days after the temperature became normal, was sufficient to control the symptoms of the disease.

The value of salicylates in the symptomatic management of acute rheumatic fever is well established. On the basis of the suggestion that the activity of salicylate depends upon its biologic oxidation product, gentisate, Meyer and Ragan administered this drug to a series of patients with rheumatic fever. They noted that, despite the absence of toxic manifestations, clinical improvement ensued rapidly.

The present report details observations on the effects of sodium gentisate in the treatment of five patients suffering from acute rheumatic fever. In an attempt to evaluate the usefulness of gentisate as an antirheumatic drug, the clinical course of this group of patients has been contrasted with the clinical course of five other patients with rheumatic fever who were treated with salicylates.

Methods and Material

The patients who were to receive salicylate or gentisate were selected by alternation. The diagnosis of acute rheumatic fever was based upon the presence of fever and polyarthritis, and upon the occurrence of cardiac abnormalities, electrocardiographic abnormalities, and a rapid sedimentation rate. All patients were maintained on absolute bedrest. Other than gentisate or salicylate, treatment was identical for the 10 patients. The course of the disease was determined by the clinical manifestations, serial electrocardiograms, white blood counts, and temperature and pulse determinations. Toxic manifestations of salicylate and of gentisate were assayed on the basis of abnormal bleeding tendencies, prolonged prothrombin times, neuropsychiatric abnormalities, gastrointestinal disturbances, and alterations in renal and hepatic function.

Following is a brief resume of the ten patients treated.

Case Reports

Group I. Patients Treated with Gentisate

Case 1, E. G., a 13 year old Puerto Rican boy, had been a resident of New York City for one year. He suffered from frequent sore throats, the last occurring four days before admission, when he also developed pain and swelling of the shoulders, knees, and left ankle. On admission he was acutely ill. The temperature was 102 F., and the ventricular rate was 100. The left ankle, the left foot, the right hip, and the right shoulder were swollen, red, and tender. The heart was markedly enlarged, and systolic and presystolic murmurs were heard over the apex. He was given sodium gentisate, 2.0 Gm. every three hours. After two days of therapy, the temperature was normal, and one day later he was asymptomatic and remained so thereafter. The drug was stopped after twelve days. The sedimentation rate, white blood count, and electrocardiogram all became normal within four weeks. Despite a total of 16.0 Gm. of gentisate daily, no evidences of toxicity were apparent. He was well at the time of discharge, after six weeks in the hospital. He was watched by his own physician and by our Follow-Up Clinic, and when last seen by us, seven months after discharge, he was active, in school, and had had no recurrences. The only murmur still present was a soft apical systolic blow.

Case 2, M. P., a 13 year old Puerto Rican girl, had been living in New York City for five years. She had had frequent attacks of pharyngitis in the past. Ten days before admission she developed a sore throat and pain in both feet. At the time of admission she was acutely ill. The ankles and the small joints of both feet were tender, red, and swollen. The temperature was 102 F., and the ventricular rate was 110.
The heart was enlarged and a rough systolic murmur could be heard over the apex. She was given sodium gentisate, 1.25 Gm. every four hours. Twenty-four hours after this treatment was begun, all subjective and objective manifestations of polyarthritis had disappeared. Her temperature was normal after four days. The drug was discontinued after seven days. Four days later her temperature rose to 101 F., and the left shoulder, left elbow, and neck became tender. Gentisate was again given, this time in a dose of 2.0 Gm. every three hours. Three days later she was again both afebrile and asymptomatic. Gentisate was continued for nineteen days, and no further recurrences were observed. The electrocardiogram was normal throughout. The maximum prothrombin time was 15 seconds. There had been no gastric irritation, tinnitus, or deafness. Epistaxis was noted on one occasion during the course of therapy, but since the prothrombin time was 12 seconds at the time, it was felt that this was a manifestation of rheumatic activity rather than of gentisate toxicity. She was discharged to a convalescent home after nine weeks in the hospital, feeling quite well. She has now been there for six months, has had no recurrences of rheumatic activity, and has required no further medication. A soft systolic murmur can still be heard at the apex.

Case 3. J. C., a 14 year old Puerto Rican boy, had suffered from three previous attacks of polyarthritis and fever. A heart murmur had been present for two years. Three days before admission he complained of feverishness, sore throat, and pain in the left knee, right ankle, and right knee. On admission to the hospital his temperature was 102 F., and his ventricular rate was 120. A systolic murmur could be heard over the apex. The involved joints were swollen, red, tender, and warm. He was given sodium gentisate, 1.0 Gm. every four hours. After two days of treatment his temperature was normal, and the signs of polyarthritis had disappeared. During the second week in the hospital, while still on treatment, he developed left maxillary sinusitis. This was accompanied by a rise in the white blood cell count to 14,000. However, no signs or symptoms of rheumatic activity were present at that time. The electrocardiogram, which showed prolongation of the P-R interval on admission, became normal in seven days. The sedimentation rate fell to normal in two weeks. Gentisate was discontinued after three weeks, and he remained well thereafter. The maximum prothrombin time was 14 seconds, and tests for liver, renal, and hematologic abnormalities were negative. He was observed in the hospital for six weeks following cessation of therapy and was well at the time of discharge. He has been examined periodically in the Follow-Up Clinic, and there have been no recurrences during the six months following discharge, although the apical systolic murmur can still be heard.

Case 4. D. A., a 67 year old white woman, had suffered from migratory polyarthritis and chorea in childhood. At the age of 54 she had an attack of arthralgia and fever and was treated effectively with salicylates. Two weeks before admission she developed pain in the left hip and calf, and a rise in temperature to 102 F. For one week her left ankle had been tender and swollen. On admission she was acutely ill. Her temperature was 105 F. Her heart was enlarged and there were systolic and diastolic murmurs at the apex. Her left ankle was red, warm, and tender, and her left hip was quite tender. The sedimentation rate was 65 mm. in one hour. Sodium gentisate was given in a dose of 1.25 Gm. every three hours. One day after treatment was started her temperature was 98.6 F., and a day later all evidences of arthritis were gone. Gentisate was discontinued after seven days. Her temperature rose slightly the next day, and gentisate treatment was reinstated, this time in a dose of 2.0 Gm. every three hours. This dosage schedule was then continued for eleven days. Her temperature again subsided promptly, and remained normal until her discharge from the hospital three weeks later. Even when the patient was receiving 16.0 Gm. of gentisate daily, the prothrombin time never exceeded 14 seconds, and no abnormal bleeding tendencies or other toxic manifestations appeared. She was well at the time of discharge, and immediately thereafter she returned to work. She was watched by her private physician, and, at the present time, seven months later, she is well and has had no recurrences of rheumatic fever.

Case 5. R. C., a 13 year old white boy, had had several previous attacks of polyarthritis and fever. Two weeks before admission he developed a similar episode and was treated with salicylate for a period of four days. Three days before admission he began to complain of pain in the knees and ankles. On admission the temperature was 100 F. and the ventricular rate 100. The heart was enlarged, and systolic and diastolic murmurs were heard at the apex. The ankles and knees were warm and tender. Sodium gentisate was given in doses of 1.25 Gm. every four hours. The joint symptoms disappeared the following day and did not recur. The temperature, however, remained slightly elevated. Electrocardiographic abnormalities, present on admission, disappeared by the fifteenth day. The white blood cell count was 13,000 on admission and normal ten days later. The sedimentation rate remained elevated persistently. On the fourteenth day of treatment he developed severe pharyngitis with a temperature of 104 F. At this time the white blood cell count rose to 23,500, the sedimentation rate to 105, and the electrocardiogram again became abnormal. There were no joint manifestations, however, at this time. Gentisate was discontinued, and he was placed on penicillin and acetylsalicylic acid, 1.25 Gm. every four hours. The throat infection was controlled in three days, and ten days later the white blood count and electrocardiogram were again nor-
mal. The sedimentation rate, however, remained elevated. The same type of low-grade fever, noted when the patient was on gentisate, persisted while he remained on salicylate, which was continued for forty days. During gentisate administration the maximum prothrombin time was 15.5 seconds, and there was no evidence of toxicity. Significantly, during the period of salicylate treatment, the prothrombin time reached 22 seconds, and the patient complained of deafness and nosebleed. There was no gastric irritation, and there were no chemical or clinical signs of liver or kidney damage. He was discharged to bedrest at home with a low-grade fever. He remained in bed for an additional two months. He was seen in the Follow-Up Clinic five months after discharge, afebrile and asymptomatic, and was then able to return to school. He had received no salicylate or gentisate since leaving the hospital. The diastolic and systolic murmurs were still audible at the apex.

Group II. Patients Treated with Salicylate

Case 6, J. C., a 13 year old white boy, was entirely well until one month before admission, when he developed pharyngitis. Four days before admission he complained of pain in the ankles and fingers. When seen in the hospital, he was acutely ill with a temperature of 103 F. Systolic and diastolic murmurs were heard at the apex. The joints of the right hand and left ankle were red and tender. He was treated with acetylsalicylic acid in doses of 1.0 Gm. every four hours. The joint pains were gone in two days, and the temperature was normal in seven. The white blood count returned to normal in four days, and the initial sedimentation rate of 96 mm. dropped to 15 mm. after twenty-six days. The maximum prothrombin time was 19 seconds. There were no bleeding episodes. He complained of tinnitus during the entire course of therapy, which lasted twenty-nine days. There were no other manifestations of salicylism. He was observed in the hospital for eight weeks after cessation of therapy, and was well at discharge. He was still well, and had had no recurrences, when seen in the Follow-Up Clinic five months later. The systolic and diastolic murmurs, however, were still present.

Case 7, D. F., a 15 year old white boy, had been hospitalized on a previous admission because of acute rheumatic fever. One week before admission he had a sore throat, and four days later he developed pain in the knees and ankles. On admission he was moderately ill, with a temperature of 103 F. and a ventricular rate of 120. The murmurs of mitral and aortic stenosis and insufficiency were present. The left ankle and right knee were warm, swollen, and tender. He was started on acetylsalicylic acid, 1.25 Gm. every four hours. Two days later the joints were normal, and the following day the temperature became normal. The electrocardiogram was normal after nine days. The white blood count fell from 17,000 to 9,800 in fifteen days, and the sedimentation rate dropped from 130 mm. to normal in thirty days. The maximum prothrombin time was 21 seconds, but there were no hemorrhagic manifestations. Because of pronounced tinnitus, the dose of salicylate was reduced to 0.625 Gm. every four hours, and administration was continued for eighteen days. He was discharged at the request of his family on the nineteenth hospital day, and was febrile at home for two months, despite the continuation of salicylates by his private physician. Thereafter, he improved slowly, and, at present, eight months after discharge, he is asymptomatic and engaging in limited activity. The murmurs of both aortic and mitral valvular disease are still present.

Case 8, C. L., a 19 year old Puerto Rican girl, was well until four weeks before admission, when she developed a sore throat. Five days before admission she experienced migratory polyarthritis, involving the joints of the neck, back, knees, and ankles. On admission she was acutely and severely ill, with a temperature of 104 F. and a ventricular rate of 120. An apical systolic murmur was present. Both ankles and both knees were red, hot, swollen, and tender. She was given acetylsalicylic acid, 1.25 Gm. every four hours, and by the following morning all the joints were much improved and the temperature had fallen to 100 F. At this point massive salicylate therapy was instituted and she was given 4.0 Gm. of sodium salicylate every four hours. After a total of 16.0 Gm. she developed nausea, vomiting, tinnitus, a maculopapular rash, a splenic hemorrhage, and a psychosis. The prothrombin time reached 19.5 seconds and the drug was discontinued. The toxic manifestations cleared rapidly, and without reinstallation of therapy the clinical manifestations of the rheumatic process subsided completely. The white blood count returned to normal in six days, the electrocardiogram became normal in ten days, and the sedimentation rate dropped from 125 mm. to normal in twenty-eight days. She was observed in the hospital for four weeks after therapy was discontinued and remained asymptomatic. However, she moved from the city after discharge, and follow-up information was not available.

Case 9, N. S., a 10 year old white girl, was admitted because of the presence of fever and arthritis. At the time of admission she was acutely ill, with a temperature of 103 F. and a ventricular rate of 108. Both ankles were tender, hot, and slightly swollen, and the left knee was tender. She was given acetylsalicylic acid, 1.25 Gm. four times a day. Joint complaints disappeared in three days, the temperature fell to normal in six days, the white blood count of 26,600 dropped to 8,750 in a week, but the sedimentation rate never returned to normal. Salicylate was continued for thirty-six days. Cardiac murmurs were heard during the course of her illness and were still present when the patient was discharged from.
the hospital, a week after salicylate therapy was discontinued. The maximum prothrombin time was 21 seconds, but there were no hemorrhages. There was no evidence of gastric irritation, tinnitus, or deafness. Because her sedimentation rate was still rapid at the time of discharge, she was kept in bed at home for four weeks. She was then allowed up progressively, and three months later was able to return to school. At the present time, eight months after discharge, she is completely well, although a systolic murmur is still heard at the apex.

Case 10, H. F., a 17 year old white boy, had an attack of acute rheumatic fever five years previously and was noted at the time to have a cardiac murmur. Two days before admission he developed pain in both feet. When first seen he was acutely ill, with a temperature of 104 F. and a tachycardia at a rate of 104. The heart was enlarged, and the murmurs of mitral and aortic valvular disease were audible. The small joints of the left foot were red and tender. He was given sodium salicylate, 1.25 Gm. every four hours. The joint pain subsided completely in twenty-four hours, and the temperature was normal by the fourth day. The white blood count became normal in five days, and the sedimentation rate in seventeen. Salicylate was continued for fifteen days. The maximum prothrombin time was 14.5 seconds. Because of tinnitus, the dosage of salicylate was reduced to 1.25 Gm. four times per day, with relief of this toxic symptom. He had one nosebleed during his stay in the hospital. There were no recurrences of rheumatic fever after the salicylate was stopped, and he was well at the time of discharge. At the present time, ten months after discharge, he is still well. He is followed both by his private physician and by the Follow-Up Clinic of the Hospital. The cardiac murmurs are unchanged.

**DISCUSSION**

Table 1 shows the effects of gentisate and salicylate upon certain rheumatic manifestations. It is apparent that both drugs reduce the fever and relieve the joint pains promptly.
Furthermore, the effects of both compounds on sedimentation rate, on leukocytosis, and on electrocardiographic alterations are similar. The uniformly effective response to gentisate suggests that this drug controls the clinical manifestations of rheumatic fever as well as does salicylate. Careful and periodic follow-up examinations ranging from five to ten months are available in nine of the ten patients, and in no case, whether treated with gentisate or with salicylate, has there been a recurrence of rheumatic fever up to the present time.

We have found that 2.0 Gm. of sodium gentisate orally every three hours is sufficient to induce prompt symptomatic and rapid objective improvement. As with salicylates premature cessation of therapy is frequently followed by a recrudescence of complaints, and it is necessary to continue treatment for ten days or more after the temperature has reached normal levels.

**Table 2.—Comparison of Salicylate and Gentisate Toxicity**

<table>
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<tr>
<th>Case</th>
<th>Bleeding</th>
<th>Prothrombin Time*</th>
<th>Tinnitus Deafness</th>
<th>Gastric Irritation</th>
<th>Hematologic Abnormality</th>
<th>Urinary Abnormality</th>
<th>Liver Dysfunction</th>
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* Undiluted plasma prothrombin time in seconds; the first figure is prothrombin time of the patient, the second is that of a normal control.
† First treated with gentisate, then salicylate.

In regard to toxicity, however, gentisate possesses certain striking advantages over salicylate. This is evidenced by the fact that, following gentisate therapy, we did not encounter any suggestion of gastric irritation, deafness, tinnitus, psychosis, or skin eruption, nor did we observe any marked alteration in prothrombin time. Salicylate administration, on the other hand, was followed almost invariably by some manifestation of salicylism, and usually by a significant increase in the prothrombin time. Neither drug, in the doses employed, produced aberrations in the blood count or abnormalities in kidney function (table 2).

The metabolism of gentisate in vivo is unknown. Following the oral administration of large doses, a reducing substance appears in the urine. This substance, at least in part, is a glucuronide as determined by the Tollens' test with naphthoresorcinol. Its presence within one to two hours after ingestion of gentisate suggests that this drug undergoes rapid oxidative breakdown in the body. This fact, together with preliminary observations on the gentisate concentration in the plasma, indicates that frequent administration of gentisate is required in order to maintain adequate therapeutic blood levels.

**Conclusions**

1. In the doses employed gentisate controls the clinical manifestations of rheumatic fever as promptly and effectively as salicylate.
2. An effective dosage schedule is 2.0 Gm. orally every three hours, continued for at least ten days after the temperature becomes normal.
3. Gentisate in the above amounts does not give rise to gastric irritation, tinnitus, deafness, marked prolongation of prothrombin time, rash, psychosis, or changes in blood count, liver, or kidney function.

4. Following the administration of gentisate, a reducing substance appears in the urine which, at least in part, is a glucuronide.

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6 Unpublished data.
Sodium Gentisate in the Treatment of Acute Rheumatic Fever
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