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THE USE OF SODIUM GENTISATE IN ACUTE RHEUMATIC FEVER

BY

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SODIUM gentisate is a drug of particular value in the treatment of acute rheumatic fever, but its use is certainly not as widespread as its efficiency would seem to justify. It was therefore decided to carry out a small pilot trial employing the two more commonly used drugs, aspirin and sodium salicylate, and sodium gentisate. Whereas the results of this trial are not statistically significant, they are of decided interest in demonstrating how the latter drug compares with the two former drugs in the treatment of acute rheumatism.

Three groups of patients were used, each group consisting of three cases of acute rheumatic fever. The cases were not selected in any way as to first or subsequent attacks, presence of clinical carditis, or length of history, etc., but were just treated with one of the three drugs as they came into hospital. Brief case histories of these patients are given below.

GROUP I—ASPIRIN THERAPY

Case 1

B. V., aged 18, was admitted to hospital with a two-day history of acute pain and swelling in his right knee, followed one day later by pain in his left knee. For one week prior to these symptoms he had a "cold in the head." There was nothing relevant in his past history.

Examination revealed a temperature of 100° F., limitation of movement in both knees with an effusion in the right knee, and a soft, blowing, apical systolic murmur.

Laboratory investigations: E.S.R. 21 mm./hr. (Westergren); W.B.C. 12,900 per cu.mm. with 88 per cent. neutrophils, 11 per cent. lymphocytes and 1 per cent. monocytes; hæmoglobin was 90 per cent. (Sahli).

He was considered to have a mild attack of rheumatic fever and was started on aspirin, 20 gr. five times daily. In two days he became asymtomatic, his E.S.R. had returned to normal limits after fourteen days, and four weeks after admission his aspirin was stopped. On discharge his apical systolic murmur was gone and there was no clinical evidence of residual cardiac involvement.

Case 2

E. P., aged 21, complained of flitting pains in his knees, ankles, wrists and shoulders for two days. He had a sore throat three weeks previously. He had already had two previous attacks of acute rheumatism at the age of 10, when he was in hospital for nine months, and at the age of 15, when he was in hospital for six months.

Examination showed that most of his joints were painful on movement, but there was little swelling. There was a loud apical systolic murmur. His E.S.R. was 101 mm./hr. (Westergren); W.B.C. was 6,200 per cu.mm. with a normal differential count, and his hæmoglobin was 80 per cent. (Sahli).

Treatment was commenced with aspirin, 20 gr. five times daily. His joint pains took five days to disappear, but on the fifth day of treatment he complained of nausea and tinnitus. The aspirin was reduced to 15 gr. doses and he lost his nausea and tinnitus in several days, but developed a slight recurrence of pain in his knees and ankles. The aspirin was then increased to 20 gr. doses again. His E.S.R. fell to normal within four weeks but then steadily rose again and did not return to normal until ten weeks after admission—aspirin therapy was continued during this time. The apical systolic murmur became inaudible and there was no evidence of residual cardiac involvement.

Case 3

A. A., aged 18, was admitted complaining of pain and stiffness in both ankles following exertion, and pain in his right elbow.

On examination he was febrile, both his ankles were red, painful and swollen, and his right elbow was tender on palpation. He had marked tachycardia, a loud apical systolic murmur, and a low-pitched soft mitral diastolic murmur.

Laboratory investigations: E.S.R. 42 mm./hr. (Westergren); hæmoglobin 80 per cent. (Sahli); W.B.C. 5,000 per cu.mm., with normal differential count. He was treated with aspirin, 20 gr. five times daily, but after two days he developed anorexia and tinnitus, and his aspirin was reduced to 15 gr. doses. Tinnitus persisted and his aspirin was further reduced after three more days to 10 gr. doses. His joint symptoms took a week to disappear, and his E.S.R. was down to normal in three weeks. The mitral diastolic murmur became inaudible a few days after admission, but his apical systolic murmur remained loud and probably indicated organic mitral valve disease. Aspirin was continued for eight weeks.

GROUP II—SALICYLATE THERAPY

Case 4

R. C., aged 19, had a four-day history of flitting pains in both ankles and both knees. There was nothing relevant in his past history.

On examination he was febrile and had effusions in both his knees and ankles. There was a loud basal pericardial friction rub but no other abnormal cardiac signs.

Laboratory investigations : E.S.R. 49 mm./hr. (Westergren) ; W.B.C. 9,000 per cu.mm. with 76 per cent. neutrophils, 20 per cent. lymphocytes and 4 per cent. monocytes ; hæmoglobin 111 per cent. (Sahli).

Treatment was commenced with sodium salicylate, 30 gr. five times daily. He lost his joint pains within a week, but his effusions took three weeks to disappear. After six days of treatment he developed tinnitus and acidotic breathing, which were relieved by stopping his salicylate for forty-eight hours and giving him sodium bicarbonate, 60 gr. four-hourly. His E.S.R. became normal after four weeks of treatment. The pericardial friction rub persisted and was present on discharge from hospital. There were no other abnormal cardiac signs. Total length of salicylate therapy was ten weeks.

Case 5

A. D., aged 16, complained of pain in his jaw and both legs for several days. He said he had never had chorea or rheumatic fever.

On examination he had a temperature of 101° F., no abnormal joint signs but definite cardiac signs—an enlarged heart with a "left ventricular" type of impulse, a low-pitched, early, blowing, basal diastolic murmur and a loud apical systolic murmur. He had a pulse pressure of 60 mm. of mercury. These signs pointed to active carditis with aortic reflux.

Laboratory investigations : E.S.R. 98 mm./hr. (Westergren) ; W.B.C. 14,700 per cu.mm. with 72 per cent. neutrophils, 20 per cent. lymphocytes, 6 per cent. monocytes and 2 per cent. eosinophils ; hæmoglobin 97 per cent. (Haldane).

He was treated with sodium salicylate, 30 gr. five times daily. His symptoms disappeared in four days, but six days after treatment was commenced he began to vomit and showed slight hyperpnœa. His salicylate was reduced to 20 gr. doses and he was given sodium bicarbonate, 30 gr. with each dose. His toxic manifestations disappeared within a week. His E.S.R. took twelve weeks to become normal, but his cardiac signs did not change and he left hospital with definite evidence of aortic regurgitation. Sodium salicylate, 100 gr. and sodium bicarbonate, 130 gr. daily, were continued for four months until the boy started to get up, when the drug dosage was reduced to 60 gr. and 90 gr. respectively. Total course of treatment lasted for five months.

Case 6

R. C., aged 15, complained of anorexia, malaise, sweating and pain in his left knee and right ankle for two days. He had a sore throat five days previously. There was no relevant past history.

On examination he was febrile, and had tenderness and limitation of movement in his left knee and right ankle. He also had a soft, blowing, apical systolic murmur.

Laboratory investigations: E.S.R. 31 mm./hr. (Westergren); W.B.C. 13,900 per cu.mm. with 83 per cent. neutrophils, 12 per cent. lymphocytes, 3 per cent. monocytes and 2 per cent. eosinophils; hæmoglobin was 92 per cent. (Haldane).

He was started on a mixture of sodium salicylate, 30 gr. and sodium bicarbonate, 30 gr. five times daily. His E.S.R. took five weeks to become normal and his progress was interrupted by several attacks of tachycardia, but these disappeared with complete bed rest. Full dosage of drugs was maintained for six weeks and then the mixture was reduced to thrice daily administration. He left the hospital with no evidence of residual cardiac involvement. Total course of salicylate therapy was eight weeks.

GROUP III—SODIUM GENTISATE THERAPY

Case 7

H. A., aged 19, complained of pain in first his left ankle and then both knees, in the previous three days. He had a sore throat three weeks before admission. No relevant past history was elicited.

On examination he was febrile, had a red, swollen, tender left ankle containing fluid, and a tender right knee. His heart was normal.

Laboratory investigations: E.S.R. 49 mm./hr. (Westergren); W.B.C. 7,400 per cu.mm.—with normal differential count; hæmoglobin 110 per cent. (Haldane).

He was started on sodium gentisate, 2 grams five times daily; he lost all joint pain in two days, and his gentisate was reduced to 1 gram thrice daily. His ankle effusion was gone in three weeks. There were no toxic effects of the drug. He left the hospital with no evidence of cardiac involvement. Total length of drug therapy was six weeks.

Case 8

G. H., aged 23, had a two-week history of malaise, and flitting pains in both elbows, both knees, both hands and both feet. There was no relevant past history.

Examination showed bilateral effusion and limitation of movement in his knees and slight swelling of both ankles. There were no abnormal cardiac signs.

Laboratory investigations: E.S.R. 33 mm./hr. (Westergren); W.B.C. 9,800 per cu.mm. with 69 per cent. neutrophils, 27 per cent. lymphocytes, 2 per cent. monocytes and 2 per cent. eosinophils.

He was started on sodium gentisate, 2 grams five times daily. His joint pains disappeared in two days, and after one week his knee effusions had absorbed. His gentisate was reduced to 1 gram thrice daily, and his E.S.R. was normal in two weeks. There were no toxic effects of the drug. On discharge there was no evidence of cardiac involvement. Length of gentisate therapy was four weeks.

Case 9

R. G., aged 11, was admitted with headaches and pain in both shoulders and elbows for two days. There was no relevant past history.

On examination he was febrile, and had tenderness on palpation and limitation of movement in both shoulders. His elbows were normal. His heart was normal.

Laboratory investigations : E.S.R. 27 mm./hr. (Westergren) ; W.B.C. 5,000 per cu.mm. with normal differential count ; hæmoglobin 102 per cent. (Haldane).

He was given sodium gentisate, 2 grams five times daily. Within three days he had lost his joint pains and within two weeks his E.S.R. was normal. He had no evidence of cardiac involvement. There were no toxic effects of the drug.

DISCUSSION

Gentisic acid is a biological product of salicylate metabolism, and it is to Meyer and Ragan in America that credit is due for the first recognition that the sodium salt of gentisic acid had valuable anti-rheumatic properties (Meyer & Ragan, 1948). Its action is essentially that of salicylate, but it has the advantage of a virtual freedom from toxic effects even with very large doses of the drug.

To enable a rapid comparison to be made of the various important factors in the treatment of these cases, a table is given (Table 1). This indicates the drug used, the length of time required for relief of symptoms and fall of E.S.R. to normal, the presence of drug toxicity and the total duration of treatment.

Table 1.

Case	Drug used	Relief of Symptoms (Days)	Fall of E.S.R. (Weeks)	Drug toxicity	Length of treatment (Weeks)
1	Aspirin	2	2	None	4
2	Aspirin	5	10	Nausea, tinnitus	10
3	Aspirin	7	3	Tinnitus	8
4	Sod. salicylate	7	4	Tinnitus, acidosis	10
5	Sod. salicylate	4	12	Vomiting, acidosis	20
6	Sod. salicylate	6	5	None	8
7	Sod. gentisate	2	3	None	6
8	Sod. gentisate	2	3	None	4
9	Sod. gentisate	2	2	None	8

Taking these points in turn, it will be seen firstly that the average length of time for relief of symptoms was less using sodium gentisate than with either of the other two drugs. Similarly the average period required for a fall of E.S.R. is less with sodium gentisate.

Drug toxicity in the form of anorexia, nausea, vomiting, tinnitus or acidosis was present in two cases of each group having aspirin and sodium salicylate respectively. These toxic manifestations occurred with the usual therapeutic doses of the drugs recommended by most authorities. No toxic effects occurred

at all with the sodium gentisate even with the high dosage of 10 grams daily. Finally the average duration of the treatment was less in the gentisate group than in either of the other two groups.

It will be seen from these results that there certainly appear to be greater advantages associated with the use of sodium gentisate than with either aspirin or sodium salicylate in acute rheumatic fever. Other successful trials have been carried out by Camelin *et al.* (1950).

Other advantages are claimed for sodium gentisate, although these were not investigated in this present small trial. Apart from the virtual absence of toxic effects such as gastric intolerance, there is no tinnitus or disturbance of acid-base equilibrium and no significant increase in the prothrombin time. Furthermore, concurrent administration of sodium bicarbonate appears to cause an increased absorption and decreased excretion of gentisate in marked contrast to the accelerated excretion of salicylate under similar conditions.

The initial dosage in acute cases of rheumatic fever is usually 2 grams five times daily, but in very severe cases the dosage may even be increased to 2.5 grams six times daily. When the acute symptoms are over and clinical improvement has been achieved, the average maintenance dose is 1 gram thrice daily.

It would thus appear that sodium gentisate is the drug of choice in the therapy of acute rheumatic disease. It must be emphasized, however, that no selection of cases was employed in this trial, the cases merely being treated with one of the three drugs as they arrived in hospital. A further, more intensive investigation is certainly warranted with some attempt to classify the cases in accordance with degrees of severity, first or later attacks, and presence or absence of clinical carditis.

SUMMARY

A small pilot trial has been conducted in which a comparison was made between the use of aspirin, sodium salicylate and sodium gentisate in the therapy of acute rheumatic fever.

Sodium gentisate appeared to be superior to the other two drugs in the disease, but a further more intensive investigation is needed to assess its full clinical value.

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