MASSIVE SALICYLATE THERAPY IN RHEUMATIC FEVER

BY

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Salicylates were first advocated for the treatment of rheumatic fever by Stricker in 1896. Lees in 1903 suggested that salicylates, if used in large dosage, had a true anti-rheumatic effect, but the majority of clinicians considered that the improvement brought about by salicylate therapy was confined to the relief of symptoms. Interest in this work was reawakened in 1943 when Coburn claimed that intensive salicylate therapy reduced the period of active infection and the incidence of permanent valvular damage, and that it controlled relapses. Coburn's work stimulated reinvestigation of the problem; excellent reviews have recently been published by Manchester (1946) and Taran and Jacobs (1945), and by Parker (1948) in this country. Not all investigators confirm Coburn's work, and it has been criticized by Warren and others (1946) and by Harris (1947).

Clinical Data and Methods Used

The present study describes results of salicylate therapy on eighty recruits at three R.A.F. reception and training centres who developed rheumatic fever between April 1947, and July 1948. All were aged 18 except two, whose ages were 23 and 26. All but three were men, and fifteen (18.8 per cent.) admitted to a history of previous rheumatic fever. A history of recent upper-respiratory-tract infection was obtained in 71.2 per cent., haemolytic streptococci being cultured from a throat swab on admission in twenty-nine of fifty-five cultured (53 per cent.). An average period of 2.1 weeks occurred between the precipitating infection and the rheumatic attack.

The diagnosis was established on criteria described by Jones in 1944. Patients were strictly confined to bed and temperatures were recorded four-hourly in the acute stage. Routine cardiac examination was performed frequently, and the patients were questioned daily concerning their arthralgia. The blood sedimentation rate (B.S.R.) was estimated weekly using Westergren's method without correction for the packed cell volume, as in no case did significant anaemia develop. Plasma salicylate levels were determined by the method of Brodie and others (1944). Patients received oral salicylates until a weekly B.S.R. had been normal on three consecutive occasions. No treatment was given for a further week, and rest in bed was still enforced. If the B.S.R. remained normal gradual mobilization extending over three

months was undertaken, when, if the patient was progressing favourably, a month's sick leave was granted. On re-admission a careful clinical and radiological cardiac assessment was made before discharge. Cases were classified as showing either (a) permanent valvular damage, or (b) potential heart disease (cases in which systolic murmurs had persisted unassociated with radiological or clinical cardiac enlargement). Cases were observed for periods of from six to fifteen months.

Dose of Salicylates

Three groups of patients were studied at three station hospitals employing varying salicylate dosage. Groups were comparable in numbers, in severity, and in the incidence of previous rheumatic attacks.

Group 1.—This group consisted of twenty-five cases; in fourteen salicylates were withheld, but the rest received small doses not exceeding 100 gr. daily.

Group 2.—This group comprised twenty-nine cases receiving 200 gr. of salicylates daily without blood-level control; ten received in addition 100 gr. of sodium bicarbonate daily.

Group 3.—Group 3 contained twenty-one cases in whom adequate salicylate levels exceeding 30 mg. per cent. were maintained by massive oral therapy. Dosage in this group showed large individual variation, from 120 to 600 gr. daily, thus anticipating the complexities of salicylate dosage recently ably described by Maggioni (1948) and by Parker (1948).

We were able to confirm Parker's observations that effective salicylate therapy could only be obtained by four-hourly oral administration of freshly made salicylate solutions in doses of 18 gr. per stone of body weight. Alkalis accelerated the urinary elimination of salicylates and required an increase of 2 gr. per stone in the dose of salicylates employed. Dehydration caused a rapid increase in the serum concentration, and was prevented by ensuring that fluid intake exceeded three pints daily. Variation in the daily excretion due to an alteration of the urinary pH, a deterioration in mixtures and in the crystalline salicylate used in dispensing the mixtures, and a tolerance developing after prolonged administration, caused further difficulties. These factors necessitated frequent blood-level determinations as long as therapy was maintained.

Results of Treatment

Effect of Temperature.—In the twenty-five cases receiving minimal doses of salicylates it was found that fever persisted for an average of 22·7 days (highest 42, lowest 3). Those on moderate dosage became afebrile in an average of 5·1 days (highest 20, lowest 1), while those on massive dosage were rendered afebrile in an average of 1·9 days (highest 4, lowest 1). In massive therapy the febrile period was therefore significantly reduced and the strain on the heart was lessened.

Effect on Arthralgia.—Cases receiving little or no salicylates did not become free from pain for an average time of 22·7 days (highest 60, lowest 4); those on moderate dosage in 6·1 days (highest 50, lowest 1); the twenty-one cases receiving massive salicylate therapy became free from pain in an average of 1·9 days (highest 4, lowest 1). A significant reduction in the period of discomfort to the patient could therefore be obtained by massive treatment.

Effect on the B.S.R.—As the B.S.R. is the best single pathological test for the assessment of activity of the rheumatic state, its rate of return to normal in salicylate therapy is of particular interest.

In the twenty-five patients receiving minimal salicylate dosage the average B.S.R. on admission was 69·1 mm. per hour (highest 120, lowest 15), and it returned to normal in an average of 73·6 days (highest 250, lowest 10).

In the twenty-nine patients receiving moderate salicylate dosage the disease process appeared to be of comparable severity, for the average B.S.R. on admission was 45·7 (highest 116, lowest 12) and it returned to normal in an average of 37·0 days (highest 80, lowest 14).

The twenty-one patients on massive therapy appeared to contain more severe cases, as the average B.S.R. on admission was 73·1 mm. per hour (highest 122, lowest 25). Despite this the B.S.R. became normal in a significantly reduced period of 16·6 days (highest 30, lowest 7).

The difference between the groups can also be demonstrated if the number of patients showing a raised B.S.R. at weekly intervals is studied (Fig. 1). In Group 1 fourteen of the twenty-five patients

studied showed a raised B.S.R. after six weeks, fourteen after eight weeks, and nine after twelve weeks; and even after twenty weeks one B.S.R. still remained elevated. In the second group all but nine of twenty-nine cases studied had returned to normal in four weeks, and all but five in six weeks, and all were normal in twelve weeks. In the group receiving massive therapy all cases showed a normal B.S.R. in five weeks.

It is interesting here to describe two cases receiving moderate dosage in which B.S.R. was rapidly controlled once an adequate level was obtained (Fig. 2).

Case 1.—A 23-year-old aircraftsman was admitted with acute rheumatic fever with carditis, his B.S.R. on admission being 75 mm. per hour. He was given 200 gr. of salicylate and became rapidly free from pain and afebrile. His B.S.R. fell slowly, but after six weeks had reached 15 mm. per hour. In the next four weeks the B.S.R. steadily mounted and after ten weeks had reached 40 mm. per hour. A salicylate level done at this time was found to be only 8 mg. per 100 c.cm. of blood. With an increase of dosage to 300 gr. a therapeutic level of 40 mg. was rapidly established. Within a week the B.S.R. had fallen to normal, and the patient made an uninterrupted recovery.

Case 2.—An 18-year-old recruit developed acute rheumatic fever with carditis and was admitted with a B.S.R. of 108 mm. per hour. He was given 200 gr. of sodium salicylate and became rapidly afebrile and free from pain. There was a slow undulant fall in his B.S.R., and after six weeks it remained at 75 mm. per hour. An estimation of the salicylate content of the plasma at this time showed it to contain 8 mg. per 100 c.cm. The dose was increased to 300 gr. daily and a therapeutic level of 42 mg. was quickly reached. There was a rapid fall in the B.S.R. which reached 28 mm. per hour in one week and became normal in three.

There are some objections to assessing salicylate effects on the B.S.R. It has been shown that massive salicylate therapy will cause significant falls in the B.S.R. in non-rheumatic conditions. Falls have been produced in tuberculosis (Rapoport and Guest,

FIG. 1.—Rate of return of B.S.R. to normal on varying salicylate dosage.

FIG. 2.—Rapid fall in B.S.R. on establishing adequate salicylate level.

1946), in carcinomatosis (Homburger, 1946) and in tuberculosis and rheumatoid arthritis (Harris, 1947). The number of cases studied, however, was small, the falls in B.S.R. produced were not of the order seen in rheumatic fever, and the B.S.R. tended to rise sharply when therapy was suspended. Five cases suffering from tuberculous pleural effusions were given large doses of salicylates. In four a significant reduction of the B.S.R. occurred, up to 40 per cent. of the initial figure, but all the

B.S.R.s rose sharply when therapy was discontinued. An investigation is proceeding on larger numbers of non-rheumatic cases to see if the reduction of the B.S.R. produced by salicylate therapy is a non-specific effect due to alterations of the plasma proteins or a true anti-rheumatic effect.

Effect on Relapses.—Both Coburn (1943) and Manchester (1946) claimed that polycyclic relapses were significantly reduced in cases receiving massive salicylate therapy. In the present series six relapses occurred in the control group, one in the moderate-dose group, and four in the massive-dose group. Although the number of cases here is too small to draw definite conclusions it would not appear that a significant reduction of relapses had been produced by massive salicylate therapy.

The effects of the drug on fever, arthralgia, B.S.R., and relapses are summarized in Table 1.

Effect on Carditis.—The present survey was not of sufficient length to assess whether the incidence of permanent cardiac damage had been reduced. It is interesting to compare the figures obtained by previous authors; these are summarized in Table 2. In the short time surveys so far reported there would seem to be much difference in the results obtained, and the figures quoted by Coburn must be considered on the optimistic side. A long-term survey with controls over a period of years would be required to make sure if permanent cardiac damage can be reduced by massive therapy.

Effect on Pericarditis.—It is in acute rheumatic pericarditis that salicylate therapy exerts a dramatic effect. Warren and others (1945), in an otherwise unenthusiastic paper on salicylate therapy, agree that in acute pericarditis salicylates appear to exert an anti-rheumatic effect. Four cases of pericarditis were seen in this series and responded well. One case in whom a steady therapeutic level was found difficult to maintain is of particular interest here as it shows the beneficial effect of salicylate on both pericarditis and B.S.R.

TABLE 1
VARIOUS EFFECTS OF SALICYLATE THERAPY

Group	No. of cases	Previous rheumatic fever	Dosage of salicylate (in gr. daily)	Days before afebrile	Days before free from pain	Average B.S.R. on admission. In mm./hr.	Days before normal	Relapses
Group 1	25	4	14 Nil ; 11 less than 100	19.6	22.6	69.1	73.6	6
Group 2	29	6	200	5.1	6.1	45.7	37.0	1
Group 3	21	5	120-600	1.9	1.9	73.1	16.6	4

Case 3.—An 18-year-old recruit was admitted with acute rheumatic fever, his B.S.R. on admission was 96 mm. per hour. He received 200 gr. of salicylates and became rapidly free from pain. The blood level after two days was 37 mg. One week after admission the B.S.R. had fallen to 70 mm., but at this time he developed precordial pain and pericardial friction. A week later his B.S.R. had fallen to 40 mm., friction was still present, and it was found that the blood salicylate level was now only 18 mg. At the beginning of the third week the B.S.R. remained unchanged, friction persisted, and the salicylate level was now only 12 mg. per 100 c.cm. of blood. Salicylate dosage was accordingly increased to 300 gr. and was maintained at this level for the

FIG. 3.—Salicylate effect in a case of rheumatic pericarditis.

next two weeks. This caused a dramatic fall in the B.S.R. to 8 mm. per hour, and friction disappeared a few days later. Salicylate levels on this dosage were found to be 40 and 35 mg. per 100 c.cm. After five weeks, in view of the improvement of the patient, dosage was reduced to 200 gr. Two days later friction recurred, and it was found that the B.S.R. had risen sharply to 40 mm. per hour and that the blood salicylate level had fallen to 15 mg. per 100 c.cm. The establishment of a therapeutic blood level of 35 mg. per 100 c.cm. again caused a rapid fall in the B.S.R. and disappearance of friction a week later.

The dose was again reduced after eleven weeks, causing the blood level to fall to 8 mg. per 100 c.cm. Again friction recurred, this time unaccompanied by a rise in the B.S.R. With an increase in dosage, friction again disappeared. Therapy was continued until the end of the sixteenth week. At the eighteenth week mobilization was followed by a sharp increase in the B.S.R. unaccompanied by any symptoms. The administration of 300 gr. of salicylate again caused a rapid fall in the B.S.R., although a steady fall in salicylate

level was observed, an example of tolerance commonly seen in cases receiving salicylates for long periods.

The case is summarized in Fig. 3.

Other Observations

A few general observations may be made here. Salicylate is most effective when commenced early in the disease, and if administration is delayed for several weeks less dramatic effects are obtained. The drug appears to become less and less effective in the treatment of polycyclic relapses. A low-grade type of infection with a subacute arthritis and low B.S.R., and without carditis verging on the rheumatoid type, was seen in this series in four cases, three in women, and appeared resistant to therapy in moderate dosage.

Toxic Effects

The beneficial effects of massive salicylate therapy must be weighed against possible toxic effects. These have recently been reviewed by Graham and

TABLE 2
EFFECTS OF SALICYLATE THERAPY ON CARDITIS

	Coburn (1943)		Manchester (1946)			Warren and others (1946)			Keith and Ross (1945)		Present series		
	No. cases	% V.D.	No. cases	% V.D.	% P.H.D.	No. cases	% V.D.	% P.H.D.	No. cases	% V.D.	No. cases	% V.D.	% P.H.D.
Small dosage	63	31.9	48	13	3.9	98	4.1	4.1	29	10.3	25	8	25
Moderate „	—	—	—	—	—	—	—	—	—	—	29	17.2	14.1
Massive „	38	nil	71	7.4	13	88	3.4	3.1	57	8.8	21	nil	8.5

V.D.=Permanent valvular damage.

P.H.D.=Potential heart disease.

FIG. 4.—Salicylate effect on prothrombin concentration.

Parker (1948). These workers divided toxic effects into three groups. In the first were symptoms which are common but unimportant—tinnitus, headache, nausea, sweating, and transient vomiting—and which can be taken as an indication that the plasma level is approaching a therapeutic concentration. In the second group were symptoms which are uncommon and which individually may be serious—such as vertigo, drowsiness, mental upsets, and haemorrhage. In the third group were symptoms both common and alarming, namely severe vomiting and hyperventilation. The appearance of symptoms in the last two groups call for an immediate modification of the dose employed. Severe vomiting was seen in the present series on two occasions and marked hyperpnoea on five.

The risk of haemorrhage due to hypoprothrombinaemia was a much-feared complication of salicylate therapy. Since it was shown by Link and his co-workers (1943) that salicylic acid produced hypoprothrombinaemia in rats, which could be prevented by the addition of vitamin K, several reports of death due to haemorrhage in salicylate therapy have been reported (Troll and Menten, 1945; Graham and Parker, 1948). A study of five cases receiving massive salicylate therapy was made, prothrombin times by Quick's method being performed twice daily. A fall in the prothrombin concentration was produced which tended to become normal later. In no case did the level fall below 50 per cent. of a normal control (Fig. 4). As it has been shown that the prothrombin must be reduced to a fifth of normal before haemorrhage is likely to occur, no adequate safety margin existed. The addition of vitamin K in a dosage of 1 mg. per g. of salicylate daily will neutralize the haemorrhagic tendency (Shapiro, 1944). Vitamin K in doses of 10 mg. daily was given as a routine in cases on massive therapy; no cases of spon-

taneous haemorrhage occurred. Haemorrhage must, therefore, be considered as a rarity in the dosage commonly employed.

Summary

In the present survey eighty Service patients suffering from rheumatic fever were treated by minimal, moderate, and massive doses of salicylates. A significant reduction in the period of fever, arthralgia, and active infection was demonstrated in the group receiving massive therapy. No reduction in the relapse rate or in the incidence of carditis was seen. The dosage is discussed, and possible toxic effects considered.

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Traitement du Rhumatisme Articulaire aigu par des Doses Massives de Salicylate

RÉSUMÉ

Au cours de l'étude ci-dessus quatre-vingt malades provenant de l'Armée ont été traités par des doses faibles, modérées, et massives de salicylate. Le groupe recevant des doses massives a présenté une diminution marquée de la durée de la fièvre, de l'arthralgie, et de l'infection active. On n'a constaté aucune diminution du nombre des rechutes ni de la fréquence de l'atteinte cardiaque. L'auteur discute la posologie et examine la possibilité d'accidents toxiques.