STUDIES OF ASPIRIN TREATMENT ON RHEUMATIC FEVER

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Since there is no specific curative treatment of rheumatic fever at the present, it is important to know what treatment can subside the inflammatory process of rheumatic fever and how to prevent residual rheumatic heart disease.

From this viewpoint, the antirheumatic potency of aspirin was studied. A number of aspirin therapy in rheumatic fever have been already reported in foreign countries. However, in Japan, there are few studies of aspirin therapy, although the occurrence of rheumatic fever is increasing each year. One reason for this that Japanese people are very sensitive to aspirin.

METHODS

Among the patients with symptoms of rheumatic fever who were admitted to the hospital from January 1957 to March 1958, 12 patients were treated with aspirin, and the results were observed and used as a basis for this research. Their diagnosis of rheumatic fever was confirmed to be the Modified Jones Criteria.

These patients ranging from 14 years to 48 years, were divided into two groups. One group was given 3 g of aspirin daily and the other was given 6 g of aspirin daily accompanied with the same doses of Alumigel. From each patient serum was tested for determination of Antistreptolysin-O (ASL-O) titer, C-reactive Protein (CRP), Mucoprotein (M.P.), and protein fraction, the last of which was done by paperelectrophoresis. These laboratory studies were performed at one week and two week intervals during the hospital stay.

The changes of toxic symptoms of fever and arthralgia and the changes of acute phase reactants were then compared in both groups.

Urinary 17-KS was also measured by the Drekter's method, 2 to 3 days immediately before and after beginning the aspirin treatment. These changes were also compared between the 3 and 6 g groups. Furthermore after one dose
of 3 or 6 g of aspirin administration, the change of eosinophils counts was observed at every hour from 8.00 a.m. to 12.00 a.m.

RESULTS

The Effect of Aspirin on the Toxic Symptoms

The high fever decreased rapidly to average temperature and the arthralgia disappeared within 5 days after beginning the aspirin treatment in each case. However in one case associated with congestive heart failure, in spite of the giving of 6 g of aspirin, the high fever and severe joint pain were not improved, but when prednisolone was exchanged, these toxic symptoms disappeared and the symptoms of congestive heart failure were at last improved.

Comparing the number of days until the disappearance of high fever and arthralgia, the 6 g administration seemed to be slightly superior than the 3 g but generally, almost no difference could be seen. (Tables 1 and 2)

The Effects of Aspirin on the Acute Phase Reactants

In the vast majority of the cases in which aspirin was given 6 g daily the blood sedimentation rate (B.S.R.) dropped about 10 mm H₂O within 3 weeks. In the cases of 3 g, the B.S.R. decreased but didn't show normal value within 3 weeks.

The difference of the decrease of M.P. levels which were measured by Winzler's method, between 3 g and 6 g groups was apparent, and the decreased of M.P. levels in the latter group was markedly rapid. (Fig. 1) The normal value of M.P. was found in 60% of the 6 g group but only 25% in the 3 g within the 6 weeks after the beginning of aspirin administration. This result
of 6 g of aspirin on M.P. levels was found to be similar to that of 30 mg of prednisolone (73%).

CRP was found to become negative within the first 10 days in the vast majority of 6 g group, but in the 3 g group it was found to become negative in about 3 weeks.

In rheumatic fever, by paper electrophoresis, serum albumin was decreased and \( \alpha_2 \)-globulin and \( \gamma \)-globulin was increased. Two weeks after the beginning of aspirin administration, these conditions had a decided tendency to return to normal. (Table 3)

<table>
<thead>
<tr>
<th>Table 3.</th>
<th>Change of serum protein fractions</th>
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<tbody>
<tr>
<td></td>
<td>before</td>
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<tr>
<td>serum protein</td>
<td>7.70 ± 0.51</td>
</tr>
<tr>
<td>A/G ratio</td>
<td>0.56 ± 0.18</td>
</tr>
<tr>
<td>Al.</td>
<td>2.78 ± 0.37</td>
</tr>
<tr>
<td>( \alpha_1 )-Gl.</td>
<td>0.37 ± 0.17</td>
</tr>
<tr>
<td>( \alpha_2 )-Gl.</td>
<td>1.10 ± 0.14</td>
</tr>
<tr>
<td>( \beta )-Gl.</td>
<td>1.08 ± 0.31</td>
</tr>
<tr>
<td>( \gamma )-Gl.</td>
<td>2.34 ± 0.57</td>
</tr>
</tbody>
</table>

The Effect of Aspirin on Urinary 17-KS

The change of urinary 17-KS, which was measured during the few days immediately before and after beginning of the aspirin treatment, was not found in 3 g group. In the cases of 6 g group, urinary 17-KS was statistically increased immediately after aspirin treatment. In a few cases of 3 g group, when no change of the urinary 17-KS was seen, the exchange of 6 g brought an immediate increase. However, in other cases under the same conditions, no change was seen. (Fig. 2)
Measuring the level of serum salicylic acid at 3.00 p.m. daily, the average rate was about 15 mg/dl in 3 g group and about 30 mg/dl in 6 g group. However in some cases of 6 g it was only under 20 mg/dl, which was the usual rate seen in the 3 g group.

Therefore it was concluded that the salicylic acid level differs in each case and an increase of urinary 17-KS in the 6 g group was not able to be always seen.

The Effect of Aspirin on the Circulating Eosinophils

After the 3 g or 6 g of aspirin was given orally in one dose at 8.00 a.m., the change of circulating eosinophils counts was observed for 4 hours. At the end of this time, a decrease showed statistically only in the 6 g group (Fig. 3). In the cases which showed a clinical improvement by the 6 g daily doses, the tendency of the increase of neutrophils and the decrease of eosinophils and lymphocytes was observed during this period.

The disappearance of toxic symptoms and the rapid improvement of acute phase reactants were considered effective cases, the disappearance of only toxic symptoms, were considered slightly effective cases, and the occurrence of neither of these were ineffective cases. As shown in Fig. 4, in only effective cases, the increasing rate of urinary 17-KS was apparent, and was greater than the increasing rate of diurnal rhythms.

The Effect of Aspirin on Carbohydrate Metabolism

In all cases of rheumatic fever which were observed in this study, the fasting blood glucose contents were normal. During the aspirin treatment, no significant changes were found in the fasting blood glucose contents. The
Fig. 3 Effect of aspirin on the change of blood eosinophils counts.

Fig. 4 Increasing rate of urinary 17-KS in sufficiently effective, insufficiently effective and ineffective groups in Rheumatic Fever and Rheumatoid Arthritis.

blood glucose level was also unchanged when aspirin was taken by the normal individual. However in all 10 cases of diabetes mellitus, while the 3 or 6 g of aspirin was given, the fasting blood glucose levels and urinary glucose contents
were markedly decreased. After the aspirin administration was stopped, the fasting blood sugar level and urinary glucose content were reversed to original level or more.

Furthermore, the effects of glucose tolerance test was observed. Even in the normal individual, the increase of blood glucose level found at the glucose tolerance test was inhibited when aspirin was taken 30 minutes before this test.

In spite of their specified doses of insulin, the diabetic patients who still suffered from hyperglycemia and glycosuria, by additional doses of aspirin, these hyperglycemia were decreased near to normal level and glycosurias were lessened. In experiments with rabbits, it was proved that adrenalin hyperglycemia and cortisone hyperglycemia could inhibited by salicylate. (Figs. 5 and 6) When salicylate was given 30 minutes before the glucose tolerance test of 10 g of glucose to the normal individuals and diabetic patients, the increases of blood glucose, serum pyruvic acid and serum lactic acid levels were inhibited and the decrease of serum inorganic phosphate was also checked in both groups.

These results of aspirin on the glucose metabolisms were similar to those of thyroxine with the exception of the change of blood glucose level.

Side Effects of Aspirin

Side effects were found in two-thirds of the cases. Such effects could be found in some of 20 mg per cent or less of serum salicylic acid levels, while on the other hand side effects were not found evident in some of 40 mg per cent or more. However on the whole, it was found more frequent in the 6 g group. In the vast majority of the cases in which side effects were found, they

Fig. 5 Effect of Sod. Salicylate on Hyperglycaemia induced with Epinephrine in normal Rabbits.
Fig. 6 Effect of Sod. Salicylate on fasting blood sugar level and on body weight in rabbits treated with Cortisone.

Table 4. Side Effects of Aspirin Treatment in Rheumatic Fever and Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Items</th>
<th>Aspirin dose</th>
<th>3 g</th>
<th>6 g</th>
<th>total</th>
</tr>
</thead>
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<tr>
<td>Anorexia</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Stomachache</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>3</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Deafness</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sweat</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic tendency</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>28</strong></td>
<td><strong>30</strong></td>
<td><strong>58</strong></td>
<td></td>
</tr>
</tbody>
</table>
occurred a few days after the aspirin treatments, or within a week at the most. The symptoms of side effects are shown in Table 4. Stomach upsets and tinnitus were frequently found to occur. The former were lessened by the administration of aspirin with milk or temporary decreases of aspirin doses.

**Effects of Aspirin on Carditis**

As an index of the effects on carditis, the change of E.C.G. and the change of heart murmur were observed. The abnormal conditions of E.C.G. were found in 7 out of 12 patients, 5 had prolongation of PR-time, one had incomplete block and one had complete block. In 4 out of 5 cases in which the prolongation of PR-time was observed, this condition was found to disappear during the aspirin treatment. Incomplete block (Wenckebach) was also returned to normal. Prolongation of PR-time was found to remain in the case of complete block after the aspirin treatment. In all cases of adult patients, heart murmur was not found to disappear after the aspirin treatment. In spite of their adult rheumatic fever, in two cases treated with large doses of prednisolone in the earlier stages, the significant heart murmur was completely disappeared.

**Studies on Index of Cessation of Antiinflammatory Drugs (Chondroitin Sulfate Tolerance Test)**

The correlation between serum mucoprotein levels and the length of durations from the supposed onset to the first measurement of serum mucoprotein was observed. The average of the serum mucoprotein levels was found to be high in the group in which the above mentioned durations were within one month. In the group in which the durations were over one month, it was shown to be low. However, in rheumatoid arthritis, a chronic progressive disease, such relationship was not found. From this point of view, it was assumed that rheumatic fever may be a self-limited disease.

When the acute rheumatic fever was treated with antiinflammatory drugs, the return to normal level of acute phase reactants, particularly the disappearance of CRP, was observed to be rapid. However, when the treatment was stopped at such a time, a relapse was frequently found, therefore, the administrations of antiinflammatory drugs were necessary as long as the self-limited durations. Therefore, no definite conclusion could be given for the cessation of such drugs. Forty-eight hours after 2 cc of 3% chondroitin sulfate solution was administered intraveously, the increase of M.P. levels, was observed in normal individual in contrast to the decrease of M.P. level in active rheumatic fever. The correlation was observed between the increased or decreased ratio of serum M.P. levels and the serum M.P. levels before chondroitin
sulfate was given, but no definite relation was found to exist. This chondroitin sulfate tolerance test was given frequently during the course of the treatment. In the six cases in which the treatment was stopped after this test returned to normal, no relapse was found. However, when the treatment was stopped before their return to normal, a relapse was found in the majority of such cases.

DISCUSSION

Salicylates were used for the first time by Mc Lellan in 1876. Since then, they have been widely used as antirheumatic drugs. However, since steroid-hormone has such a marked antirheumatic potency, salicylates seem to be seldom used in the treatment of rheumatic diseases. Recent studies(1) on rheumatoid arthritis have shown no difference of antirheumatic potency between aspirin and steroid-hormone. It has also been found that salicylates seem to stimulate the pituitary-adrenal system. As a result, aspirin is again receiving the spotlight as an important drug in the treatment of rheumatic diseases.

In this study, 3 g and 6 g of aspirin had a similar dramatic effect to the toxic symptoms as fever and arthralgia etc. However, for the improvement of acute phase reactants, 6 g was definitely superior to 3 g. These evidences have suggested that a 6 g dose has some other effect other than the specific pharmacological effects of aspirin.

Heilman(2) found the same effects from large doses of aspirin as corticotropin and cortisone only in normal pituitary-adrenal system, but in hypophysectomized or adrenalectomized cases, decreasing circulating eosinophils counts was not found. Van Cauwenberge(3) proved that by large doses of aspirin, ascorbic acid content of adrenal glands was decreased in animals, but was not decreased in hypophysectomized animals. Hetzel and Hine(4), Cronheim, et al(5), found the same evidence. Raskman gave 4–6 g of sodium of salicylic acid to twelve healthy medical students with the following results: the rates of uric acid and creatinine in their urines were increased and 6 hours after this administration, the circulating eosinophils counts were markedly decreased. Bertolani et al(7) found that when 0.075 g of sodium of salicylic acid was continued daily in guinea pigs, the urine 17-KS content was found increased with the highest level 17-KS content occuring 3–4 days after beginning this experiment. Van Cauwenberge and Hensghem(8) gave 8 g of aspirin to rheumatic patients for various periods of a week to several weeks. Their plasma corticoid levels and urine reductive corticoid levels were increased in all cases, but no change of urine 17-KS levels was found. Bayliss and Steinbeck(9) reported that
salicylates given to adult rheumatic diseases, the blood 17-OHCS level was not increased, neither after one does, nor after a long continuation of the administration. Roskam and Van Cauwenberge\(^{(10)}\) found that blood 17-OHCS level was increased in hypersalicylemia of rheumatoid arthritis patients who were given large doses of salicylates for a long period. Benard\(^{(6)}\) also found the same evidence in normal adults who were orally administered 4 g of aspirin for 3 weeks, but no increase of blood free and conjugated 17-OHCS level occurred at one dose of 4 g aspirin. Pellegrini and Sala\(^{(6)}\) observed that urine 11-oxytocorticoids and 17-KS were increased in rheumatic children treated with salicylates. The histological change showing the increase of adrenocortical excretion after salicylate administration, was reported. Smith\(^{(6)}\) reported contradictory evidence that no increase of urine 17-Hydroxycorticoids was found following salicylate administration. When large doses of aspirin was experimentally given to depancreatized or depancreatized and adrenalectomized diabetic rats, the diabetic symptoms were improved. However, after the cessation of aspirin, these symptoms returned to their former condition. Therefore, Ingle\(^{(11)}\) reported that aspirin did not stimulate the pituitary adrenal system. Ungar\(^{(12)}\) found that antiinflammatory potency of salicylate was not seen in hypophysectomized animals.

In this study, in the cases of the 6 g group, urinary 17-KS was statistically increased immediately after aspirin treatment, and the circulating eosinophils counts were decreased after only one dose of 6 g aspirin. These evidences showed that 6 g of aspirin seemed to have ACTH-like effects. These effects were further supported by the fact that the increasing rate of urinary 17-KS was apparent in only effective cases. Since even 3 g of aspirin improved toxic symptoms, hypersalicylism seemed to have ACTH-like effects besides the specific pharmacological effects of aspirin. However, these ACTH-like effects were not proved from the point of carbohydrate metabolism. Therefore, the effect on carbohydrate metabolism was assumed to be part of the specific pharmacological effects.

In this research, side effects of aspirin were found in two-thirds of the cases. However, when aspirin was administered with milk, or when the dosages were reduced temporarily, most of these side effects were disappeared. Since the relationship of side effects and the blood salicylic acid level was not found, the occurrence of side effects was different in each individual. Phenol compounds with strong anti-rheumatic potency but without any side effects, such as 2, 3, 6-Trihydroxy benzoic acid found by Clark\(^{(13)}\), must be yet discovered.

The most important problem in the treatment of acute rheumatic fever is
its effect on carditis. Although previous histories of rheumatic fever and heart diseases were not found in the patients treated with aspirin in this report, due to the fact that they were young adults and adults, it was difficult to determine whether or not each case was his first attack. The disappearance of heart murmur after aspirin treatment was not found in any case. On the other hand, in two cases of adult rheumatic fever treated with large doses of prednisolone in the early stage, the significant heart murmur was completely disappeared.

One this point, it was presumed that the effect of aspirin on carditis was inferior to that of prednisolone. However, the impairment of atrioventricular conduction was improved by aspirin treatment.

No index has yet been found for the cessation of antiinflammatory drugs. The mechanism of chondroitin sulfate tolerance test has not been proved. Clinically, however, such an index was found to be sufficiently useful in this test.

**SUMMARY**

Thirteen patients with acute rheumatic fever in young adults and adults were treated with 3 g or 6 g of aspirin. Three grams of aspirin had a similar dramatic effect to the toxic symptoms of fever and arthralgia etc. as 6 g of aspirin. However, for the improvement of acute phase reactants, 6 g was definitely superior to 3 g.

Based on the study of the change of Urinary 17-KS and circulating eosinophils counts, such differences were assumed that 6 g of aspirin seemed to have non-specific ACTH-like effects other than the specific pharmacological effects of aspirin. These ACTH-like effects were not proved from the point of carbohydrate metabolism. The disturbances of atrio-ventricular conduction were improved by aspirin. Side effects of aspirin were found in two-thirds of the cases. Chondroitin sulfate tolerance test was reported as an index of cessation for antiinflammatory drugs.

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**REFERENCES**