ASPIRIN TREATMENT AND PLATELET FUNCTION IN KAWASAKI DISEASE

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The comparative effectiveness of small-dose (30 mg/kg) aspirin and high-dose (150 mg/kg) in Kawasaki disease was evaluated in clinical symptoms and platelet aggregation. Twenty-three patients with Kawasaki disease were entered in the randomized study and divided into three groups. The durations of fever were 14.8 ± 3.5 days in the control group, 11.3 ± 2.1 d. in the small-dose group and 8.7 ± 2.3 d. in the high-dose group. The high-dose group showed a significantly shorter duration of fever ($P < .01$).

The platelet aggregation induced by ADP in the second week of illness were $82.4 \pm 11.6\%$ in the control group, $66.8 \pm 9.6\%$ in the small-dose group and $88.0 \pm 10.7\%$ in the high-dose group ($69.0 \pm 5.0\%$ in healthy children). The control group and high-dose group showed significantly increased aggregation as compared with healthy children. The platelet aggregation in small-dose group was significantly lower than that in the control group ($P < .01$). SGOT and SGPT elevated in half of the patients treated with high dose of aspirin. In Kawasaki disease, 30 mg/kg/day of aspirin is recommended to prevent arterial thrombi.

INTRODUCTION

Kawasaki disease (mucocutaneous lymph node syndrome, MCLS) is an acute febrile illness of infants and young children associated with characteristic mucocutaneous involvement and cervical lymphadenopathy. It is estimated that, since it was first reported by Kawasaki in 1967 (Kawasaki et al., 1967), more than 15,000 cases of this disease have occurred in Japan up to 1978. The etiology of this disease remains obscure and no rational treatment measures are available as of today. The most important clinical problem is sudden death from coronary arteritis accompanied by aneurysms and thrombotic occlusion (Kato et al.,

1975). The approximate mortality rate is 1.4%. Our previous study, however, has demonstrated that aspirin was effective on coronary lesions in Kawasaki disease (Kato et al., 1979). In addition, 30 mg/kg dose of aspirin showed a suppressing effect on the hyperaggregability of platelet in this disease, and it has been considered to be useful to prevent the formation of arterial thrombi (Yokoyama et al., 1977). In this study, we attempted to use high doses of aspirin such as that used in collagen vascular disease, expecting its anti-inflammatory effects. The comparative study on the effectiveness of small or high doses of aspirin in Kawasaki disease was evaluated in clinical symptoms and platelet aggregation.

PATIENTS AND METHODS

Twenty-three patients diagnosed as Kawasaki disease according to the guidelines (Table 1) at Kurume University Hospital were entered in the randomized study of small-dose versus high-dose aspirin therapy. The age of these patients ranged from 3 months to 6 years and there were 14 males and 9 females. They were divided into three

groups treated with three different regimens; 7 patients were treated with antibiotic (50mg/kg/day of cephalexine) only for one week (control group), 30 mg/kg dose of aspirin was administered to 9 patients daily until coronary angiography was performed (small-dose group) and 100-150 mg/kg dose of aspirin was administered to 7 patients until serum salicylate levels reached 25 mg/100 ml and/or the appearance of

TABLE 1

Diagnostic guideline of Kawasaki disease (August 1978)

A. PRINCIPAL SYMPTOMS

1. Fever of unknown etiology lasting 5 days or more
2. Bilateral congestion of ocular conjunctivae
3. Changes of lips and oral cavity
 - (1) Dryness, redness and fissuring of lips
 - (2) Protuberance of tongue papillae (strawberry tongue)
 - (3) Diffuse reddening of oral and pharyngeal mucosa
4. Changes of peripheral extremities
 - (1) Reddening of palms and soles (initial stage)
 - (2) Indurative edema (initial stage)
 - (3) Membranous desquamation from fingertips (convalescent stage)
5. Polymorphous exanthema of body trunk without vesicles or crusts
6. Acute nonpurulent swelling of cervical lymphnodes of 1.5 cm or more in diameter

At least five items of 1~6 should be satisfied for diagnosis of MCLS.

B. OTHER SIGNIFICANT SYMPTOMS OR FINDINGS

1. Carditis, especially myocarditis and pericarditis
2. Diarrhea
3. Arthralgia or arthritis
4. Proteinuria and increase of leukocytes in urine sediment
5. Changes in blood tests
 - (1) Leukocytosis with shift to the left
 - (2) Slight decrease in erythrocyte and hemoglobin levels
 - (3) Increased ESR (4) Positive CRP (5) Increased α_2 -globulin
 - (6) Thrombocytosis (7) Negative ASO
6. Changes occasionally observed
 - (1) Aseptic meningitis
 - (2) Mild jaundice or slight increase of serum transaminase
 - (3) Swelling of gall bladder

Remarks: 1. Male Female ratio: 1.5/1, patients under 5 years of age: 80%, fatality rate: 1~2 % (usually sudden death due to coronary thrombosis), recurrence rate: 2~3 %.

2. Complication after recovery: occasionally myocardial infarction and mitral insufficiency.

3. Autopsy: coronary aneurysm, thrombosis and myocarditis in most cases.

any sign of salicylate intoxication. The platelet count and platelet aggregation were determined every week in all cases. In some cases, serum salicylate levels at two hours after ingestion of aspirin were determined every three days by Keller's method (Keller, 1947). The number of platelets was counted by Brecher-Cronkite technique. Platelet aggregation was estimated from changes in optical transmission of citrated platelet-rich plasma at 37°C with a concentration of 400,000/mm³ using Bryston aggregometer. As an inducer of aggregation, ADP (final concentration, 4.8×10^{-6} mol) was used. The de-

gree of platelet aggregation was evaluated as the rate of maximal aggregation regardless of time.

RESULTS

Platelet counts in the second or third week of illness were elevated in all cases (Fig. 1). The maximum value ranged from 580,000/mm³ to 1,140,000/mm³ ($809,000 \pm 142,000/\text{mm}^3$). The number of platelets started increasing in the second week of illness, reached a peak at around the third week and returned to a normal range at the fifth week of illness. There was no difference between the control group and groups treated by small dose or high dose aspirin. Platelet aggregation was accelerated from the second week to the fourth week of illness in the control group, and its average value was $82.4 \pm 11.6\%$ in the second week of illness (Fig. 2). The platelet aggregation was significantly increased compared with that in healthy children ($69.0 \pm 5.0\%$). In the small-dose group, the average value of platelet aggregation was $66.8 \pm 9.6\%$ in the second week of illness and $64.7 \pm 7.1\%$ in the third week of illness (Fig. 2). These values were significantly lower than that of the control group ($P < .01$). Meanwhile, in the high-dose group, the average value of the platelet aggregation was $88.0 \pm 10.7\%$ in the second week of illness. There was no significant difference between the high-dose group and the control group. In seven patients given 150 mg/kg dose of aspirin, serum salicylate levels were low, ranged from 1.9 mg/100 ml to 16.0 mg/100 ml (9.3 ± 4.6 mg/100 ml) in the 7th day of the illness. However, at the third or fourth week of the illness when acute manifestations disappeared, serum salicylate levels increased significantly and reached to 40.0 mg/100 ml in one case.

Fig. 1. Changes in platelet counts in patients with Kawasaki disease.

Fig. 2. ADP-induced platelet aggregation in patients with Kawasaki disease. Stippled area indicates platelet aggregation in healthy children (mean $\pm$ S.D.).

The average duration of fever (above 37°C) was 14.8 ± 3.5 day in the control group, 11.3 ± 2.1 day in the small-dose group and 8.7 ± 2.3 days in the high-dose group. The high-dose group showed a significantly shorter duration of fever ($P < .01$). 1/7 cases (14%) in the control group, 8/16 cases (50%) in the small-dose group and 2/8 cases (25%) in the high-dose group had improved in erythrocyte sedimentation rate by the third week of the illness. There was no significant difference between the small-dose group and the high-dose group.

DISCUSSION

Thrombocytosis in Kawasaki disease was first reported by Asai and coworkers

(Asai et al., 1973). The mechanism of thrombocytosis and platelet hyperaggregability in Kawasaki disease remains elusive. This thrombocytosis and hyperaggregability may be caused by the association with angitis and/or the presence of the immune-complex. In our investigation, 27/150 cases (17%) showed coronary aneurysms on coronary angiography (Kato et al., 1979): in these cases, thrombocytosis and hyperaggregability could lead to formation of arterial thrombi. It is recognized that platelet aggregation plays a major role in initiation of an arterial thrombus (Weiss, 1975). According to our results, platelet aggregation was suppressed in the small-dose group; on the other hand, it was not suppressed in the high-dose group. This fact may be explained by the hypothesis that a small dose of aspirin inhibits the generation of thromboxan A_2 which is inducer of platelet aggregation, and furthermore, a high dose of aspirin inhibits vessel wall production of PGI_2 (prostacyclin) as well, which is an inhibitor of platelet aggregation (Kelton et al., 1978). A high dose of aspirin was given to seven patients, expecting its anti-inflammatory effect as well as antithrombotic effect. It is accepted that serum salicylate levels of 20 to 30 mg/100 ml are required for the optimal anti-inflammatory effect in patients with rheumatic disease. However, serum salicylate levels were markedly lower, contrary to our expectation in the acute phase. But when acute manifestation disappeared, serum salicylate levels had begun to rise rapidly and reached 40 mg/100 ml in one case. This suggests that Kawasaki disease patients had malabsorption of aspirin during the acute phase, which was already reported by Jacobs (Jacobs, 1978). The high-dose group revealed a significantly shorter duration of fever as compared with the

small-dose and control group ($P < .01$). However, elevated ESR and positive C-reactive protein did not return to normal even after the disappearance of fever, which was not significant compared with the small-dose group. The ultimate purpose in the treatment of Kawasaki disease is not to shorten the duration of fever, but to reduce coronary abnormalities and to prevent the formation of arterial thrombi. Although high doses of aspirin have some effects on fever in Kawasaki disease, it is rather detrimental in preventing arterial thrombi because of its thrombogenic effect (Kelton et al., 1978). In addition, careful monitoring of patients treated with high doses of aspirin is necessary to predict salicylate intoxication, and SGOT and SGPT elevated in the half of those patients treated with high dose aspirin who we observed. However, further evaluation by coronary angiography should be necessary. In conclusion, the authors recommend that aspirin be administered in Kawasaki disease in doses of 30 mg/kg per day.

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