Further review of aspirin in the treatment of Kawasaki disease

Abstract

Aspirin only prevents platelets from accumulating in the dilated coronary arteries and prevents thrombosis, thus minimizing thrombosis as much as possible, and does not shrink the already dilated coronary artery tumor. Therefore, it plays an important role in the treatment of Kawasaki disease, but it is not the cause of treatment. Aspirin is common in the treatment of kawasaki disease in children, and its effect is to reduce acute inflammatory response and alleviate platelet aggregation. Aspirin has been used to treat Kawasaki disease for more than 50 years. Since 1961, when Kawasaki discovered the first reported case of hemorrhagic shock caused by aspirin in children with Kawasaki disease, we need to re-examine the use of aspirin in the treatment of Kawasaki disease.

Key words: Aspirin; Kawasaki disease; Coronary artery damage

Introduction

Ⅰ. Overview and History:

Aspirin: known as an antipyretic and analgesic.Aspirin was first used to Anti-rheumatism medicine in the 1960s and 1970s (100~150mg), and then it became anti-inflammatory and anti-thrombotic. Some people think that there is no difference between low dose and high dose of aspirin in the treatment of acute KD. [19] Found in the willow Tree plant in 1800, aspirin is one of the oldest painkillers in the world. Its original name is salicylic acid, which means acid. Around 1900, http://BAYER.CO's company named aspirin and found sodium and acetyl chloride in acetylsalicylic, two compounds that reduce swelling and comfort the stomach.

Aspirin belongs to antipyretic and analgesic drugs, salicylic acid derivatives, can be used to relieve mild or moderate pain (such as toothache, headache, neuralgia, muscle pain), can also be used for cold, flu and other febrile diseases, treatment of rheumatism and pain. In addition, aspirin has an inhibitory effect on platelet aggregation, and can also be used to prevent transient ischemic attack, myocardial infarction, artificial heart valve and venous fistula or other postoperative thrombosis, and is one of the commonly used drugs in the treatment of Kawasaki disease.

Kawasaki disease: Mucocutaneous lymph node syndrome (MCLS) is a disease named after Tomisaku Kawasaki, a doctor in Japan who first reported it in 1967. The disease is a systemic vasculitis as the main pathological changes of acute fever exanthema children's disease. The age of high incidence is under 5 years old infants, more male than female, adults and children under 3 months of age rarely. Clinical manifestations may include fever, rash, non-purulent lymph node enlargement in the neck, hyperemia of eye binding membrane, diffuse hyperemia of oral mucosa, erythema of bayberry tongue, palm and

foot, and rigid edema. This disease has attracted people's attention because of its serious cardiovascular complications, and the incidence of untreated children is 20% to 25%.

Acute treatment includes intravenous infusion of gamma globulin, oral aspirin, hormones, etc. 1). Intravenous gamma globulin therapy can reduce the incidence of coronary aneurysm complications. The usage is single dose intravenous drip, 10 ~ 12 hours input. The recommended time of administration is 5 to 10 days after onset. The incidence of coronary aneurysm increased after 10 days. The symptoms of fever and other inflammatory reactions recovered rapidly within 1 to 2 days after treatment. 2) aspirin oral administration: divided into 3 to 4 times for 14 consecutive days, and then reduced to a large dose, or reduced to a small dose after 3 days of fever; 3) glucocorticoids: only used for the second-line treatment of children with non-response to intravenous gamma globulin infusion.

The main therapeutic objectives of kawasaki disease convalescence period are anticoagulant, thrombolytic, prevention of myocardial infarction and relief of coronary artery stenosis and occlusion and other serious cardiovascular complications. The main drugs to treat thrombotic diseases are: first, anti-platelet drugs; Heparin drugs; Third, long-acting anticoagulant drugs; Fourth, fibrinolytic and thrombolytic drugs.

The use of aspirin in Kawasaki disease is very important and plays a vital role in the recovery period of the disease. In the initial acute phase, take 30 to 50 mg/kg in 2 to 3 doses daily. After the use of heat, three days began to gradually reduce, about two weeks reduced to 3~5 mg/kg per day, at least to maintain 6~8 weeks. If you have coronary artery disease, you need to extend the medication until the coronary artery completely returns to normal. Aspirin is used to prevent coronary artery disease. Prevention of coronary artery aneurysms plays a crucial role, as well as preventing blood clots.

The role of aspirin in the long-term treatment of kawasaki disease children is well known, but often some parents of kawasaki disease children in the clinic say to the doctor, my child has been treated with aspirin for so long, why is the coronary artery still dilated? To answer this question, parents need to understand the role of kawasaki disease treatment. The harm of children with kawasaki disease is coronary artery expansion, even form of coronary artery aneurysms, internal blood flow will slow down, easy to cause expansion of thrombosis, expanding blood clots can block blood flow after slowly, once the vessel is completely blocked by a blood clot, there will be one of the most serious consequences, namely myocardial infarction, or coronary artery aneurysm rupture can endanger the patient's life. Aspirin only prevents platelets from accumulating in the dilated coronary arteries and prevents thrombosis, thus minimizing thrombosis as much as possible, and does not shrink the already dilated coronary artery tumor. Therefore, it plays an important role in the treatment of Kawasaki disease, but it is not the cause of treatment.

Ⅱ. Pharmacological action and Chemical structure:

Aspirin is a representative antipyretic analgesic anti-inflammatory drugs, chemical name is 2-(acetoxy) benzoic acid, structure is C9H8O4.

First of all, aspirin is a non-steroidal anti-inflammatory drug. Its specific pharmacological effect is to inhibit cycloxygenase, reduce the synthesis of prostaglandin, thromboxane and

other inflammatory mediators. It has antipyretic analgesic and anti-inflammatory effects. Can be used for fever, joint pain, headache, toothache, can also be used for rheumatic diseases as an adjunctive treatment. Do not pass at present most often use at, prevent the occurrence of thrombotic sex disease such as myocardial infarction, cerebral infarction. The specific pharmacological mechanism is that aspirin can inhibit the synthesis of thromboxane in platelets, thus inhibiting platelet agglutination and preventing thrombosis.

Ⅲ. Metabolism and bioavailability:

Aspirin enteric-coated tablets are absorbed quickly and completely after oral administration. Absorption has begun in the stomach and can be absorbed mostly in the upper small intestine. Absorption and solubility are related to gastrointestinal pH. Food can reduce absorption rate but does not affect absorption amount. Enteric-coated tablet agent absorbs slowly. Aspirin enteric-coated tablet is absorbed quickly when taken with sodium bicarbonate. After absorption, it is distributed in various tissues and can also penetrate into the joint cavity and cerebrospinal fluid. The protein binding rate of aspirin is low, but the binding rate of hydrolyzed salicylate protein is 65% ~ 90%. The binding rate decreases with high plasma concentration. The incidence of renal insufficiency and pregnancy was also low. T1/2 is 15-20 minutes; The length of T1/2 of salicylate depends on the dose size and urine pH value, and is about 2-3 hours for a small dose. High dose can be more than 20 hours, repeated use of up to 5 to 18 hours. After a single oral administration of 0.65g aspirin, the salicylate t1/2 in milk was 3.8 ~ 12.5 hours.
Most aspirin enteric-coated tablets are rapidly hydrolyzed to salicylate in the gastrointestinal tract, liver, and blood, and then metabolized in the liver. The main metabolites were salicyluric acid and glucuronic acid conjugate, and a small part was oxidized to Gentisic acid. The blood drug peak value is reached 1-2 hours after one dose. The blood concentration of analgesia and antipyretic was 25-50 μg/ mL. Anti rheumatism, anti inflammation 150 ~ 300μg/ mL. The time required for plasma concentration to stabilize increases with the daily dose, typically 7 days for high doses (e.g., anti-rheumatism), but 2-3 weeks or more are needed to achieve optimal efficacy. In patients with long-term high dose medication, because the main metabolic pathway of drugs has been saturated, a slight increase in dose can lead to a large change in blood drug concentration. Aspirin enteric-coated tablets are excreted from the kidney with bound metabolites and free salicylic acid. When the dosage is larger, the excretion of unmetabolized salicylic acid increases. There can be a lot of discrimination between individuals. The excretion rate was accelerated in alkaline urine, and the amount of free salicylic acid increased, but it was the opposite in acidic urine.

Ⅳ. Pharmacological and pathological clinical effects of Kawasaki disease:

Aspirin is common in the treatment of kawasaki disease in children, and its effect is to reduce acute inflammatory response and alleviate platelet aggregation. Kawasaki disease, also known as cutaneous mucosal lymph node syndrome, is an acute, systemic, vascular

inflammatory disease that tends to involve medium and large arteries, especially coronary arteries [6]. The main effect of aspirin is to reduce acute inflammation and reduce platelet aggregation. Taking aspirin can reduce acute inflammation of blood vessels and avoid coronary artery disease. The drug can better inhibit the activity of cycloxygenase, and has a better blocking effect on thrombosis and prostaglandin generation, anti-inflammatory and anticoagulant effect is good, and the drug has fast onset and stable efficacy, high clinical application value. However, it has been found in clinical practice that the effect of single drug therapy is limited and can be combined with other drugs [5].

Ⅴ. Similarities and differences of aspirin tolerance and toxic and side effects between European and American races and Asian people

Around 1970, British scientists studied why acetylsalicylic is effective and won a Nobel Prize. In the short term, aspirin has antipyretic, analgesic and anti-inflammatory effects, but in the long term, aspirin is also a kind of anti-stroke, anti-heart attack medicine.

There are three types of aspirin commonly used in hospitals. One is swallowed in tablet form, 100 mg, another is water soluble tablet form, 300 mg, and the other is capsule form, which is opened in addition to the powder and there is an aspirin tablet in the capsule with a dose of 375 mg. In this case, the average patient who was preventive and had a history of heart disease was 100 mg per day. If the patient's EKG changes or there are signs of heart failure, the doctor will immediately order 300 milligrams. If the patient has had a TIA (small ischemic stroke) they should take 375 mg for a long time. In medical wards, 8 to 9 out of 10 patients typically take aspirin for a long time. One can imagine the importance of aspirin in long-term prevention and health care.

Since 1988, aspirin has been used to prevent first strokes and first heart attacks. But there can also be serious bleeding side effects, gastrointestinal bleeding or even brain bleeding. Doctors generally assess whether aspirin should be taken even at risk. The Oxford University Antithrombotic Clinical Trial group used a sample of 95, 000 patients: 0.51 percent of these cardiovascular patients took aspirin for a long period of time, while the other half did not take aspirin. The results showed a 20 percent reduction in the rate of first heart attack and stroke among aspirin users, but bleeding rates ranged from 0.07 percent to 0.10 percent among aspirin users.

Aspirin was developed in 1899, and its antiplatelet effect was not discovered until the 1970s. At present, aspirin has been widely used for grade 1 prevention of cardiovascular and cerebrovascular diseases. Studies have shown that aspirin can increase the risk of cerebral hemorrhage. Several multi-center, large sample and controlled studies have been conducted in Europe and the United States, with different results. However, large-scale studies in this regard are still lacking in China. There is no significant difference in the efficacy of low-dose aspirin and high-dose aspirin in grade 2 prevention of cardiovascular and cerebrovascular diseases. Although the incidence of gastrointestinal side effects of low-dose aspirin is smaller than that of high-dose aspirin, foreign studies have shown that reducing aspirin dose does not significantly reduce the incidence of bleeding.

The incidence of cerebral and gastrointestinal hemorrhage in Asian race is higher than

that in western race. Does aspirin use increase the risk of bleeding more in Asians than in Europeans and Americans? Relevant studies have shown that Asian people are safe for small doses of aspirin (≤100mg/d) in drug dose research center, but moderate to high doses of aspirin (≥300mg/d) may increase the risk of cerebral hemorrhage and digestive tract hemorrhage in Asian people [6-7].

Ⅵ. Recently, a multi-country study in five countries, including the United States, Britain and France, found that small doses and large doses have the same effect on Kawasaki disease

To evaluate the antiplatelet aggregation function and methods of aspirin in children with Kawasaki disease. The clinical data of children with Kawasaki disease admitted to Peking University Capital Institute of Pediatrics teaching Hospital from September 2016 to September 2018 were analyzed. All the children were routinely treated with aspirin, with high dose (30-50)mg/(kg·d) in the acute phase and low dose (3-5)mg/(kg·d) in the recovery phase. Light transmission was applied Aggregometry (LTA) determined platelet aggregation rates at different doses of aspirin to evaluate its antiplatelet aggregation function, and statistical methods were used to analyze the risk factors for aspirin resistance (AR). The results of (1) The platelet aggregation rate (AA %) of children with Kawasaki disease after oral high-dose and low-dose aspirin treatment was 3.3% (1.2%, 7.1%) and 2.9% (1.5%, 6.4%), respectively. There was no significant difference in the inhibitory effect of different doses of aspirin on platelet (AA %) (P=0.174) The incidence of AR was 9.75% (23/236) in the forest group and 8.5% (19/236) in the low-dose aspirin group, and the difference was not statistically significant (P=0.617). In the low-dose aspirin group, 19 patients had AR and 217 aspirin-sensitive patients had ASPIRIN Sensitivity,AS) there were no significant differences in age, gender, coagulation, biochemistry and other related indexes of the children. Conclusion The antiplatelet aggregation function of aspirin in children with Kawasaki disease is independent of dose. AR exists in the treatment of Kawasaki disease, and the incidence of AR is independent of dose.

The poor drug resistance or response of Kawasaki disease to aspirin therapy is a clinical problem that can not be ignored. By analyzing the polymorphism of clotting related genes in children under 5 years old, an independent indicator of coronary artery injury can be determined by detecting the PEAR1 genotype alone, which is conducive to guiding clinical rational drug use and avoiding unnecessary side effects [10-12].

Ⅶ. Kawasaki disease + aspirin has recently been reported to lead to a gradual increase in nasal bleeding and gastrointestinal bleeding cases

Although aspirin can effectively prevent and cure cardiovascular and cerebrovascular diseases, it is not suitable for everyone. Aspirin should not be taken by people with stomach and duodenal ulcers, which can cause bleeding or perforation. Patients with coagulation disorders such as severe liver damage, hypoprothrombin, vitamin K deficiency, etc. Children with viral infection and fever should not be used. It has been

reported that children and adolescents under 16 years old suffering from influenza, chickenpox or other viral infections, and then taking aspirin, can appear serious liver insufficiency combined with encephalopathy symptoms.

With some drugs: with vitamin B1, can increase gastrointestinal reactions; When used together with D860, it is easy to cause hypoglycemic reaction. Combined with adrenal corticosteroids, easy to induce ulcers; When used with furosemide, it is easy to cause salicylic acid poisoning.

Long-term use: Even in small doses, may damage the gastrointestinal mucosa and may cause ulcers, which may lead to bleeding or perforation. In particular, aspirin inhibits platelet aggregation, which can lead to significant bleeding.

Complications of Kawasaki disease include coronary artery dilation, coronary aneurysms, thrombosis, resulting in arterial stenosis and myocardial ischemia, and even fatal heart failure and encephalopathy[8-9].

Aspirin has been used to treat Kawasaki disease for more than 50 years. Since 1961, when Kawasaki discovered the first reported case of hemorrhagic shock caused by aspirin in children with Kawasaki disease, we need to re-examine the use of aspirin in the treatment of Kawasaki disease. There is no denying that aspirin plays an important role in Kawasaki disease, but it is time to determine what dose is appropriate for Kawasaki disease through different periods of high, medium and low intensity.Although high-dose aspirin shortens the duration of fever, treatment without aspirin in the acute phase has no influence on the response to IVIG, resolution of inflammation, or the development of CALs. In the IVIG era, high-dose aspirin may provide little benefit to the treatment in the acute phase of KD.[20]

Ⅷ. Is there any difference between low-dose aspirin and high-dose aspirin

The cause and pathogenesis of Kawasaki disease are still unknown. It is speculated to be related to infection and abnormal immune response. In acute stage, there is obvious immune disorder, CD4/CD8 increase, which makes the body's immune system in an over-activated state. Early use of gamma globulin can make CD8 increase, CD4 decrease, thereby reducing IgG synthesis, block vascular endothelial immune inflammatory reaction, so to shorten the course of disease, reduce complications, improve the cure rate plays an important role.

Gamma globulin can largely reduce the probability of coronary artery lesions, it could be with antigen antibody neutralization, then to mononuclear cells play a role of inhibition of the expression of PDGF - 13, at the same time, it also can inhibit T cell activation, and in improving the endothelial cell apoptosis, promote microbial toxin and its role in immune regulator. Moreover, the drug can block Fc receptor, further block the immune response on the surface of blood vessels, inhibit the secretion of cytotoxin, interfere with platelet adhesion and agglutination, and ultimately inhibit the formation of thrombus. Therefore, the drug has a good inhibitory effect on coronary artery disease.

It has been reported[3] that the dose of gamma globulin is 400mg/(kg.d) for 5 days, and the effect is slowHigh-dose single dose therapy can not only quickly promote the recovery

of acute vasculitis and improve symptoms, but also effectively prevent the occurrence of coronary aneurysm, reducing its incidence from 20%-25% to less than 5%. Coronary artery dilatation improved significantly in most patients after 2 weeks of single dose treatment. These results suggest that gamma globulin can promote repair of coronary artery dilation [(2)].

Platelets were normal in the acute phase and elevated at week 3. Routine oral administration of aspirin after gamma globulin therapy prevents platelet aggregation and thrombosis, but aspirin has not been proven to prevent coronary aneurysms [(13)]. At present, most people advocate a small dose of 30-50mg/(kg.d), divided into three oral. This dose has less adverse effects on liver and gastrointestinal tract [(14)].

Ⅸ. Conclusion and prospect

Aspirin has been used for kawasaki disease for more than 50 years and has long been used as an adjunct treatment for kawasaki disease. In the acute phase of Kawasaki disease, high dose aspirin (80-100mg/kg.d) is used in the United States, while moderate dose aspirin (30-50mg/kg.d) is used in Japan and Western European countries, which is replaced by low dose aspirin (3-5mg/kg.d) after 48-72h of heat withdrawal, and oral administration continues for 6-8 weeks. In children with coronary artery damage, oral administration is required until the coronary arteries are normal. Although moderate and high dose aspirin can reduce inflammatory response in the acute phase of Kawasaki disease, it is controversial whether it can reduce the incidence of coronary artery damage and propyl ball resistance. At present, there is no evidence for the duration of aspirin administration according to the conventional 6-8 weeks of heat loss. In addition, adverse reactions (including nosebleed, gastrointestinal hemorrhage, subcutaneous hemorrhage and intracranial hemorrhage) have been reported in children with Kawasaki disease treated with aspirin, and the optimal dose and timing of aspirin administration are also controversial [(15)].

A number of recent studies have shown that, compared with low-dose aspirin, medium-dose and high-dose aspirin have no advantage in preventing coronary artery injury [1,15]. Dhanrajani et al. [11] treated kawasaki patients at two Canadian centers with IVIG combined with low-dose aspirin and IVIG combined with high-dose aspirin, respectively, and found that the incidence of IVIG resistance in the low-dose aspirin group was 3 times higher than that in the high-dose aspirin group (23% versus 8.7%), but the length of hospital stay and coronary outcomes were both significant Aneurysm (coronaryarteryaneurysms, CAA) (Z value of 2.5 or higher) rate of no significant difference. High-dose aspirin may not only fail to reduce the occurrence of coronary artery injury, but also be associated with the high incidence of coronary artery injury in kawasaki disease children. Kim et al. [16] included 8456 children with Kawasaki disease from the eighth Kawasaki disease survey in South Korea, and analyzed the effect of medium-dose and high-dose aspirin on CAA prevention in the treatment of acute Kawasaki disease. Univariate analysis and multivariate Logistic analysis showed that medium-dose and high-dose aspirin were risk factors for CAA. Similarly,Amarilyo et al. [17] also mentioned in their study that the incidence of coronary artery damage in the high-dose aspirin group

was significantly increased and the hospital stay was longer. Therefore, it was believed that high-dose aspirin in the acute phase of Kawasaki disease had no significant clinical benefit and should be used with caution. In addition, aspirin may be used for too long. Yoo et al. [18] found that low-dose aspirin should be used in children with Kawasaki disease after heat withdrawal until all inflammatory indicators and thrombosis markers were normal (3-4 weeks on average) and no cardiovascular complications were observed, and the drug should be discontinued after 6-8 weeks of follow-up. No new coronary artery damage occurred except in children with coronary artery damage in the acute phase. These results indicate that the application of aspirin for 6~8 weeks after heat withdrawal may be too long.

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