Ticlopidine Plus Aspirin for Coronary Thrombosis in Kawasaki Disease

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ABSTRACT. Selective inhibitors of the adenosine 5'-diphosphate pathway of platelet activation have been used rarely in children in the United States. We report the successful use of ticlopidine, together with aspirin, in a 7-month-old infant with Kawasaki disease complicated by a thrombus in a giant coronary aneurysm that failed to resolve with thrombolytic therapy. Pediatrics 2000;105(5). URL: http://www.pediatrics.org/cgi/content/full/105/5/e64; Kawasaki disease, coronary aneurysms, antithrombotic therapy, ticlopidine, children.

ABBREVIATIONS. LAD, left anterior descending coronary artery; IV, intravenous; ADP, adenosine 5'-diphosphate.

Ticlopidine is an antiplatelet drug that has been used in several clinical settings in place of or in combination with aspirin.1,2 Although ticlopidine has been used as routine antiplatelet therapy in children in Japan,3 its use in children has been minimal in the United States. We report here the successful use of ticlopidine as an antiplatelet agent in a 7-month-old infant with Kawasaki disease complicated by a thrombus in a giant coronary artery aneurysm that failed to respond to thrombolytic therapy.

CASE REPORT

A previously healthy 4.5-month-old Gypsy male presented to an outside center with a 7-day history of fever, extremity swelling, and nonexudative conjunctivitis. Echocardiography showed marked dilation and aneurysm of the left and right coronary arteries, and a diagnosis of Kawasaki disease was made. The patient was treated with intravenous γ-globulin (2 g/kg) and high-dose aspirin. He was discharged after 2.5 weeks on aspirin (20 mg every day) and dipyridamole (2.5 mg 3 times daily). Three months after illness onset, echocardiography at our institution demonstrated a giant aneurysm (9 mm maximum diameter) of the left anterior descending coronary artery (LAD), which was partially occluded by a large thrombus. The patient had no evidence of myocardial ischemia or infarction. Thrombolytic therapy with t-PA (5 mg/kg/hour intravenous [IV]) was administered for 19 hours, without diminution in clot size as assessed by serial 2D echocardiography. Subsequently, the patient was treated with streptokinase (1500 units/kg IV) bolus followed by 1500 units/kg/hour IV for 48 hours, also without detectable effect. Chronic anticoagulation with warfarin was rejected because of the parents’ concerns about its risk and the discomfort of therapeutic monitoring, as well as doubts by the medical team regarding the family’s compliance with frequent laboratory testing. As a result, an alternative antithrombotic therapy with oral ticlopidine (8 mg/kg twice daily) and low-dose aspirin (20 mg every day) was initiated. The patient was discharged on the fifth hospital day.

Nine days after hospital discharge, 2D echocardiography demonstrated similar size of the LAD thrombus (Fig 1A); 2 weeks later, the thrombus had virtually disappeared (Fig 1B). The patient continued on ticlopidine and aspirin, and his neutrophil count and liver function test results remained normal. By 13 months after illness onset, the LAD aneurysm had decreased to <5 mm in diameter, and ticlopidine was discontinued. The patient remains on low-dose aspirin.

DISCUSSION

Kawasaki disease is an acute childhood vasculitis of unknown cause characterized by fever, rash, conjunctivitis, inflammation of the mucous membranes, swollen erythematous hands and feet, and cervical adenopathy.4 Coronary artery aneurysms or ectasia develop in ~15% to 25% of affected children.5 High-dose IV γ-globulin therapy has been demonstrated to be safe and effective in reducing the prevalence of coronary artery abnormalities when administered early in the course of Kawasaki disease.6,7 Even with such treatment, however, ~5% of patients develop coronary abnormalities, with male infants at the highest risk.5 Aneurysm size tends to diminish over time, but progressive stenosis may be produced by marked myointimal proliferation.8 Early coronary thrombosis occurs almost exclusively among patients with giant aneurysms (internal diameter ≥8 mm).9 After thrombolytic therapy, long-term antithrombotic prophylaxis typically includes warfarin anticoagulation with low-dose aspirin.10 However, oral anticoagulation with warfarin is difficult to regulate, particularly in young children, and its risks increase when compliance with treatment and monitoring is poor. Therapy with a potent antiplatelet agent may be a viable alternative under these circumstances.

Ticlopidine acts as a selective inhibitor of the adenosine 5'-diphosphate (ADP) pathway of platelet activation, decreasing the capacity of ADP to induce the conformational changes in glycoprotein IIb/IIIa complexes that allow these complexes to bind fibrinogen and thus mediate platelet aggregation.11 Ticlopidine has been suggested to be more effective than aspirin in the prevention of strokes in high-risk patients and, in conjunction with aspirin, to reduce the incidence of both cardiac events and hemorrhagic and vascular complications after coronary artery stenting in comparison to conventional anticoagulant...
therapy. Adverse effects, however, particularly severe neutropenia in 1% to 2% of patients, which is not always reversible after cessation of the drug, have prevented ticlopidine from replacing aspirin as the therapy of choice in the United States for stroke prevention. Since the treatment of this patient, however, clopidogrel has emerged as an alternative inhibitor of platelet aggregation, which in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events trial had similar efficacy to aspirin with an extremely low risk of myelotoxicity.

The mechanism of clot disappearance on ticlopidine only 3 weeks after failure of high-dose thrombolytic therapy is uncertain. Antiplatelet therapy with inhibitors of ADP-induced activation of the glycoprotein IIb/IIIa pathway might prevent expansion of an existing thrombus or the formation of new clots. Ticlopidine might exert an immediate thrombolytic effect separate from its delayed antiplatelet action, possibly through the release of endothelial prostacyclin and/or tissue plasminogen activator. Kawasaki disease is known to be associated with a state of hypercoagulability and platelet activation, which can persist for weeks after the onset of fever. It is most likely that, during the period after the failure of t-PA and streptokinase, as the patient recovered from a hypercoagulable state, ticlopidine may have prevented further thrombosis and allowed the LAD thrombus to be lysed by intrinsic fibrinolytic activity.

CONCLUSION

In summary, therapy with inhibitors of ADP-induced platelet aggregation, although rarely used in children in the United States, may be added to aspirin therapy as a practical alternative for pediatric patients who are difficult to regulate on oral anticoagulants for medical or social reasons. In addition, these medications may provide effective antiplatelet therapy for Kawasaki patients who develop giant aneurysms and are at high risk for thrombotic occlusion of coronary arteries. Controlled, prospective, multicenter studies would be desirable to evaluate the efficacy and safety of inhibitors of ADP-induced platelet aggregation in children with Kawasaki disease.

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