Safety and Efficacy of Clopidogrel in Children with Heart Disease

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Objective  To evaluate the efficiency and safety of clopidogrel treatment in children with heart disease.

Study design  We conducted single center retrospective chart review of children with heart disease at the University Hospital, Leuven, Belgium, in whom clopidogrel was used. The indication, dosage, duration of therapy, and adverse events were examined. Clinical efficacy was defined by an absence of thrombotic events.

Results  46 children were identified. The mean age of first clopidogrel dose was 4.9 ± 4.1 years. The study dosage ranged from 0.1 to 0.7 mg/kg/day clopidogrel. Almost all patients received concomitant aspirin therapy. No thrombotic events developed. Skin bruising developed in almost every patient, suggesting that clopidogrel has an anti-platelet effect. 2 patients who were treated with concomitant warfarin had bleeding complications (severe epistaxis and gastrointestinal bleeding). Hematological abnormalities were documented in 1 patient who received clopidogrel for 1 year; they reversed with medication cessation.

Conclusion  Clopidogrel therapy in a pediatric population appears to be relatively safe and effective; however, randomized, controlled prospective studies are needed to determine the true efficacy and safety of clopidogrel in children. (J Pediatr 2008;153:61-4)

The use of antiplatelet drugs for the primary and secondary prevention of cardiovascular and cerebrovascular thromboses in adult populations has been evaluated, resulting in defined management guidelines.1-4 Much less is known about the use of antiplatelet drugs in infants and children for secondary prevention of ischemic stroke, prevention of coronary artery thrombosis in Kawasaki disease, or prevention of thromboembolism after surgery for congenital heart disease.5 The use of low-dose aspirin (ASA) is often advocated for these conditions; however, good scientific evidence for its safety and efficacy does not exist. ASA alone, however, may not be sufficient to prevent thrombosis, because it only blocks the cyclooxygenase pathway, leaving other platelet activation pathways unaffected.6 There is very little experience with other anti-platelet treatments in children. Clopidogrel, a thienopyridine derivative, is a potent oral anti-platelet agent often used in conjunction with ASA for the treatment of coronary artery disease, peripheral vascular disease, and cerebrovascular disease in adults.7,8 Combined with ASA, clopidogrel provides an additive antiplatelet effect.

There is very limited published information about the use of clopidogrel in children, and the currently available literature is limited to case reports and reviews of case series.9-11 Currently, more information is needed on the safety and optimal dosage of clopidogrel in children with congenital/pediatric heart disease. This report describes our experience with clopidogrel in pediatric heart disease patients.

METHODS

The data gathered for this analysis is retrospective. This report has been prepared in accordance with the ICH Harmonized Tripartite Guideline on the Structure and Content of Clinical Study Reports, dated July 1996. Patient confidentiality was ensured by using patient initials on the case report form in lieu of the patient’s name.

Patients in the study were selected when they had received clopidogrel in our cardiology unit since 2000, and the parent or guardian of the child had given prior written informed consent for the use of any clinical data for research proposes in accordance with the requirements of our local ethics committee. All patients started taking clopidogrel during hospitalization (either after an operation or an interventional catheterization). The drug was given as a single daily dose of between 0.5 and 1.0 mg/kg/day, with patients observed for 24 hours. The daily dose was subsequently lowered to 0.2 to 0.3 mg/kg/day.
For dosing <32.5 mg, the pharmacy crushed the tablets, and the prescribed dose was prepared in capsules. The parents were instructed to dissolve the content of these capsules into a small quantity of milk or juice and administer this once a day just before the feeding. The timing of the drug administration was different for each patient. Most of the patients received concomitant medication.

Patient charts were reviewed for the indication, dosage, duration of off-label use of clopidogrel, and any adverse events that occurred during the period of treatment. Study clinical efficacy was defined as the absence of any clotting events. Care was taken to evaluate all possible thrombotic events; these include shunt occlusion, stent occlusion, thrombi in Fontan conduits, or thrombosis at cavopulmonary connections. Serious adverse events were defined as death potentially related to the medication, bleeding complications apart from skin hematomas, thrombosis, and allergic reactions. Adverse events associated with bleeding were also documented. Normally after hospital discharge and therapy initiation, patients are seen after 1 month in the outpatient clinic for complete clinical and cardiologic evaluation. After this initial visit, the follow-up differed in different types of patients.

RESULTS

46 children (29 male, 17 female) were included in this study. Most patients were Caucasian (n = 45); 1 patient was of unknown race/ethnicity. The mean age at the first dose was 4.9 ± 4.1 years (median age, 3.9 years; age range, 7 days-15 years). The mean weight at first administration of the drug was 19.0 ± 14.9 kg (median weight, 15 kg; weight range, 3.6-72 kg). Most patients (44/46) were treated because of congenital heart disease: 36 patients had a functionally univentricular heart, 3 patients had a form of tetralogy of Fallot, 2 patients had truncus arteriosus, 2 patients had pulmonary venous stenosis, and 1 patient had an atrial septal defect. 1 of the 2 remaining patients was treated because of Kawasaki disease with giant aneurysm formation on the right coronary artery with proximal coronary artery stenosis; the other patient was treated after coil occlusion of a large arteriovenous malformation originating from the subclavian artery. 44 patients had undergone surgery. In patients with complex univentricular physiology (n = 36), multiple palliative procedures were often performed. In 32 of the 46 patients, anti-platelet treatment was started after a surgical procedure during hospitalization (26 after total cavopulmonary connection, 5 after bidirectional Glenn shunt), and in 1 patient anti-platelet treatment was started after modified Blalock-Taussig shunt. 14 of 46 patients were treated after interventional catheterization (10 after stent implantation, 2 after coil implantation, 2 after femoral artery thrombosis). 43 of 46 patients were receiving concomitant ASA in a single dose of 0.5 to 5 mg/kg/day. 2 patients received concomitant warfarin in addition to ASA and clopidogrel. In 3 patients, aspirin was not added to the treatment: in 2 patients because warfarin was already added to the treatment and in 1 patient because clopidogrel monotherapy was started after coronary artery stent implantation. The timing of the drug administration was different for each patient. In interventional patients, the drug was started within 24 hours after the catheter intervention. In patients who underwent surgery, the drug was generally started within the first 2 weeks after the operation.

Safety Evaluation

The mean duration of clopidogrel exposure was 132.7 ± 139.9 days, with a range of 1 to 833 days. The daily dose of clopidogrel was between 0.1 and 0.7 mg/kg (mean, 0.41 ± 0.15 mg/kg), which was adjusted on a patient-by-patient basis and reduced when any adverse events occurred. During initial use of clopidogrel, doses of 0.5 to 1.0 mg/kg/day were used, on the basis of the expected dose extrapolated from adult dosing. During the study period reviewed, doses were subsequently lowered to 0.2 to 0.3 mg/kg/day because of the development of recurrent epistaxis in 1 patient. 1 patient who was also taking warfarin had serious bleeding complications, including 1 patient with severe epistaxis and 1 patient with gastrointestinal bleeding. Clopidogrel was stopped in both patients. No thrombotic events or clots could be detected in any of the treated patients. Most Fontan patients underwent a cardiac catheterization with transesophageal echocardiography within 6 months after the Fontan operation, and thrombi could not be detected in any patient. There were also no thrombotic events during treatment in the shunt or stent patient population.

10 of the 46 patients had a drug-related adverse event, including serious adverse events, and 9 patients permanently withdrew from treatment because of these events. 1 patient died because of recurrent pulmonary venous stenosis unrelated to the clopidogrel therapy. Pulmonary venous stenosis developed in this patient after surgical correction of total abnormal pulmonary venous return. The patient was not amenable to any surgical or medical treatment; stents implanted during the surgical intervention rapidly re-stenosed despite clopidogrel treatment. Death was caused by right heart failure and low cardiac output. The other patients reported adverse events that resulted in patient withdrawal from the study, although the relationship to clopidogrel treatment was not always evident. The reported events included epistaxis (n = 2), allergic reaction (n = 2), hair loss (n = 1), skin bruising causing parental concern (n = 2), melena (n = 1), and hematological abnormalities including anemia and reduced white blood cell count (n = 1).

Minor bleeding complications were most common, but no serious bleeding complications were observed that required hospitalization or urgent medical treatment. There were no associated petechiae or purpura. Gingival bleeding was not reported in our patients. 2 patients experienced recurrent epistaxis; 1 of these patients was taking concomitant warfarin. This complication was thought probably to be related to clopidogrel use and resolved when the dose was lowered in 1 patient and the drug was stopped in the second patient. Most patients or their parents reported easy skin bruising, especially in the lower extremities, during the combination treatment...
with ASA and clopidogrel. This was considered a normal physiological phenomenon reflecting the efficacy of the treatment at the current dose and not considered as an adverse event unless it was the specific cause for treatment cessation. The parents were reassured about this finding. We did not have the clinical impression that the bruising was any worse than that in patients treated receiving low-dose ASA only. The parents of 2 patients were very concerned about the easy skin bruising, and, for them, it was a reason to stop clopidogrel treatment and continue on ASA only. This reduced the problem, but did not completely resolve it. Melena developed in 1 patient while the patient was taking concomitant warfarin. After stopping clopidogrel, the melena resolved. This complication was probably related to concomitant clopidogrel use.

Apart from the bleeding complications, other adverse events were recorded in 4 patients. 2 patients experienced an allergic skin reaction early after the drug was initiated. In 1 patient, this occurred after the first dose; it was characterized by the development of erythema, itching, and some allergic papules. In the second patient, the skin allergy occurred after 13 days of treatment. The allergic phenomena regressed quickly after clopidogrel was withdrawn, and no serious allergic reactions were observed. In both patients, this was considered to be related to the drug treatment. Hair loss was observed in 1 patient after being hospitalized for a coronary stent implantation. She received a drug-eluting stent with Taxol. It is unclear whether the hair loss was related to clopidogrel, caused by Taxol, or caused by stress associated with the procedure. Clopidogrel was stopped, and hair loss quickly recovered. This was possibly related to clopidogrel use. Hematological abnormalities thought to be possibly related to clopidogrel use were observed in 1 girl after prolonged clopidogrel use (365 days). She had a low hemoglobin level (7.6 g/dL) and low white blood cell count (2.2 × 10^9/L) with neutropenia and lymphopenia. The platelet number was relatively well preserved (167 × 10^9/L). The girl complained of chronic abdominal pain, and she was observed in hospital for the abdominal symptoms. She was on concomitant furosemide, aldosterone, and lisinopril. During this period, a bone marrow aspiration was performed to further assess the hematological abnormalities. This showed a normocellular bone marrow. She had low serum iron (31 μg/dL), a low MCV (73 fL), and a low transferring saturation (6%). The red blood cell morphology was consistent with microcytic, hypochromic anemia. This showed the presence of iron deficiency anemia, but this could not explain the low white blood count and relatively low platelet count. It was suspected that clopidogrel use could potentially influence the hematological abnormalities. Iron treatment was also started. After stopping clopidogrel and adding iron, the hematological variables normalized within 2 weeks.

Clinical laboratory investigations were not systematically undertaken in this patient cohort. However, many patients underwent laboratory testing (especially the Fontan group), and no specific abnormalities were shown.
data suggest additional therapeutic benefit of combining fibrinolysis with ASA, clopidogrel, and enoxaprin in patients with ST elevation myocardial infarction without significantly increasing the bleeding risk.12 This also needs further investigation in pediatric patients, but should be approached cautiously.

Thrombotic thrombocytopenia purpura is the most commonly reported hematologic adverse effect with clopidogrel, although neutropenia, acquired hemophilia, isolated thrombocytopenia or idiopathic immune thrombocytopenia, and thrombotic thrombocytopenia purpura with hemolytic uremic syndrome are other rare-yet-recognized hematologic adverse effects. Early recognition and prompt initiation of rescue treatment can be life-saving in such patients. In our study, anemia and a low white blood cell count developed in 1 girl who received prolonged clopidogrel treatment. Extensive testing failed to identify an underlying cause, although blood values returned to normal within 2 weeks of discontinuing clopidogrel. Careful monitoring of hematological variables is recommended during the first 2 to 3 months and for those receiving chronic treatment, every 2 to 3 months.

No thrombotic events were observed in this small case series. According to earlier reports in patients with congenital heart disease and systemic-to-pulmonary artery shunts, shunt thrombosis can be expected in as many as 12% of patients. In postoperative Fontan patients, thrombotic events have been reported in as many as 33% of patients.13 On the basis of these data, we would have expected thrombotic events in 2 to 15 patients in this study. The additional use of ASA may have further reduced thrombotic risk. ASA has demonstrated both survival benefits and reduced risk for shunt thrombosis in patients after a systemic-to-pulmonary artery shunt and has also been reported to reduce the rate of occlusion of aorto-pulmonary shunts in a small case series (n = 37).14 However, the efficacy of ASA was not confirmed in a larger study of 478 pediatric patients.15 Furthermore, there is a paucity of data on the long-term efficacy and safety of low-dose ASA in children. No thrombotic events were reported in the other recent retrospective study in 15 children aged 6 weeks to 16 years (median age, 3.5 years) who received 1 to 6 mg/kg/day of clopidogrel for 1 to 6 months.9,10

Our study has limitations. It is a retrospective review of patient charts from 1 institution, and clinical laboratory testing was not systematically undertaken; however, available laboratory results showed no specific abnormalities. The tablets were crushed, thus the exact dose administered could not be accurately determined. There are no available pharmacodynamic data on crushed clopidogrel tablets; however, the tablet formulation is not known to interact with food or concomitant medications.8 The small sample size and the varied timing of drug administration for each patient are also relevant when evaluating our results.

The results of prospective randomized trials such as PICOLO and CLARINET are eagerly awaited. These studies will more clearly establish the optimal dosage, efficacy, and safety of clopidogrel in pediatric patients and to define responsiveness in different age groups and disease subtypes in this high-risk population.

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REFERENCES