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Clopidogrel for Platelet Inhibition in Pediatric Patients

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Clopidogrel was approved by the Food and Drug Administration (FDA) on November 11, 1997 for the prevention of thrombosis in adults with acute coronary syndrome, recent stroke or myocardial infarction, or established peripheral arterial disease.^{1,2} Although not approved for use in pediatric patients, clopidogrel has been used for over a decade to prevent thrombosis in children with cardiac diseases predisposing them to clot formation or after ischemic stroke, cardiac catheterization, or implantation of intracardiac or intravascular stents or devices.

Clopidogrel has recently been in the news with the March 12th announcement by the FDA of a new black box warning calling attention to pharmacogenomic studies which have identified reduced efficacy in poor metabolizers of the drug.³ This issue of *Pediatric Pharmacotherapy* will describe the available studies on clopidogrel in pediatric patients, discuss the implications of pharmacogenetic differences on the efficacy of treatment, and review its adverse effects, drug interactions, and dosing recommendations.

Mechanism of Action and Pharmacodynamics

Clopidogrel, a thienopyridine derivative, is a prodrug that undergoes metabolism by cytochrome P450 enzymes to form an active thiol metabolite. This metabolite acts as a selective irreversible inhibitor of P2Y₁₂ adenosine diphosphate (ADP) receptors on platelets, blocking ADP-mediated activation of the glycoprotein GPIIb/IIIa complex and as a result, inhibiting platelet aggregation.^{1,2}

Clopidogrel inhibits aggregation for the life of the platelet, typically 7 to 10 days. It produces a dose-dependent effect, beginning 2 hours after a single dose and reaching steady-state after 3 to 7 days of treatment. After standard dosing in adults, the degree of platelet inhibition is approximately 40 to 60%. Platelet function and bleeding time typically return to baseline values within 5 days after discontinuation.

Pharmacokinetics

Clopidogrel is rapidly absorbed after oral administration, with a bioavailability of approximately 50%. Food does not affect absorption. Clopidogrel undergoes metabolism through cytochrome P450 enzymes 2C19, 3A, 2B6, and 1A2, as well as hydrolysis via plasma esterases. The latter mechanism produces inactive carboxylic acid derivatives and makes up approximately 85% of circulating clopidogrel metabolites. Metabolism through hepatic cytochromes results in the production of an intermediate metabolite, 2-oxo-clopidogrel, which undergoes subsequent metabolism to form the active thiol derivative.^{1,2}

The maximum serum concentration of the active thiol metabolite occurs approximately 30-60 minutes after administration of a clopidogrel dose. The half-life of the parent compound is 6 hours in adults, while the half-life of the active metabolite is approximately 30 minutes.^{1,2}

Pharmacogenomics

Formation of both 2-oxo-clopidogrel and the thiol metabolites is dependent on CYP2C19. Recent pharmacogenomic studies have demonstrated that clopidogrel concentrations as well as antiplatelet effects, as measured by platelet aggregation assays, vary according to CYP2C19 genotype. The CYP2C19*1 allele is fully functional, while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. Other alleles (including CYP2C19*4 through CYP2C19*8) result in reduced metabolism.

Patients with two copies of loss-of-function alleles are poor metabolizers and are typically unable to produce adequate concentrations of the active thiol metabolite. It has been estimated that 2 to 14% of U.S. population are poor metabolizers. Function appears to vary by ethnicity, with nonfunctional CYP2C19*2 and CYP2C19*3 alleles responsible for 85% of Caucasian and 99% of Asian patients classified as poor metabolizers.^{1,2,4,5}

In a study of adults receiving 75 mg clopidogrel once daily for 5 days, thiol metabolite concentrations ranged from 16-18 ng/mL in ultrarapid, extensive, and intermediate metabolizers, while the average concentration in the poor metabolizer group was only 7 ng/mL. Measurement of inhibition of platelet aggregation likewise revealed a substantial difference in the poor metabolizer group. Using the vasodilator-stimulated phosphoprotein-platelet reactivity index (in which lower numbers represent greater inhibition), the ultrarapid, extensive, and intermediate group had values ranging from 20-29%, compared with a value of 61% in the poor metabolizers.^{1,4}

The impact of CYP2C19 variation has also been demonstrated in clinical trials. In the majority of cohort studies conducted to date, poor metabolizers (and in some studies, intermediate metabolizers as well) have had a higher rate of adverse cardiovascular outcomes, including death, myocardial infarction, or stroke. Based on these studies, the FDA has added a black box warning to the prescribing information for clopidogrel highlighting the risk for reduced efficacy in poor metabolizers and recommending the use of alternative antiplatelet drugs in these patients. The black box warning serves to strengthen the original warning added to the prescribing information in May 2009. While not mandating genetic testing, the black box warning indicates that tests are available to determine a patient's CYP2C19 status. Several companies are advertising CYP2C19 testing on the Internet, with costs ranging from \$235-\$429.^{1,4}

Pediatric Clinical Trials

In 2005, Finkelstein and colleagues published the first case series of clopidogrel use in children.⁶ The authors conducted a retrospective study of 15 patients 6 weeks to 16 years of age who received clopidogrel between January 2001 and April 2004. The median patient age was 3.5 years; four of the patients were under 1 year of age. All patients had underlying cardiovascular disease. Fourteen of the children started therapy after cardiac catheterization. Of these, 10 received clopidogrel as primary thrombosis prevention after stent insertion, three others had clot formation after catheterization, and one child was switched from their previous therapy with heparin after development of a hematoma at the catheterization site. The average clopidogrel dose was 2.3 ± 1.3 mg/kg (range 1 to 6 mg/kg). No loading dose was given. Patients requiring doses less than 75 mg received individually prepared capsules. Clopidogrel was continued for up to 6 months. Concomitant therapy included aspirin in 12 children, enoxaparin in five children, and warfarin in two children. At follow-up (3 weeks to 12 months), 11 children

had no evidence of thrombosis or stent obstruction. One patient, a 6-year-old treated with clopidogrel, warfarin, and aspirin, developed a major gastrointestinal bleed after one month of therapy. Based on their results, the authors suggested that clopidogrel may be a useful in children and merited further study.

The following year, Soman and colleagues conducted a retrospective study of clopidogrel in 17 children with ischemic stroke.⁷ The patients ranged in age from 1 to 16 years. Eight children were treated with clopidogrel alone and nine received clopidogrel and aspirin. The dose of clopidogrel ranged from 0.8 to 2.4 mg/kg given once daily. Treatment was discontinued after 6 to 12 months. At follow-up, none of the patients had experienced a stroke recurrence. Four of the combination therapy patients discontinued treatment because of complications, including hand numbness, headache, post-operative bleeding, and a subdural bleed. The authors concluded that clopidogrel was a reasonable option for children who were unable to take aspirin or failed to respond to aspirin. They suggested that the combination of clopidogrel and aspirin be used with caution after stroke.

The results of the first clinical trial of clopidogrel in pediatric patients, the Platelet Inhibition in Children on Clopidogrel (PICOLO) trial, were published in 2008. This international, multicenter, prospective, randomized, placebo-controlled trial was designed to evaluate the pharmacodynamic profile of clopidogrel in infants and young children and establish an optimal dose. The goal was to achieve a mean inhibition of ADP-induced platelet aggregation of 30 to 50%, similar to the effect produced by a clopidogrel dose of 75 mg in adults. Patients were randomized to receive clopidogrel at a daily dose of 0.01 mg/kg, 0.1 mg/kg, 0.15 mg/kg or 0.2 mg/kg) or placebo for a period of 7 to 28 days. A total of 73 infants and children (0-24 months of age) completed the study. The majority of the patients were also taking aspirin.

The study revealed a dose-related response to clopidogrel, with the 0.2 mg/kg dose achieving an average of 49.3% inhibition of the maximum extent of platelet aggregation and an average of 43.9% inhibition of the rate of platelet aggregation. As in adult studies, there was considerable interpatient variability. Clopidogrel was well tolerated; two patients in both the clopidogrel and the placebo groups developed minor bleeding. There were no serious bleeding events reported.⁸

The efficacy and safety of clopidogrel 0.2 mg/kg/day is now being studied in the Clopidogrel to Lower Arterial Thrombotic Risk

in Neonates and Infants Trial (CLARINET). This multicenter, randomized, placebo-controlled trial has completed enrollment and is being followed by an 18-month extension study in infants who still had their systemic-to-pulmonary artery shunt in place at one year of age.⁸

Two additional retrospective studies have been published since release of the PICOLO data, but both reflect clopidogrel dosing prior to the availability of the PICOLO trial results.^{9,10} Mertens and colleagues described 46 children with cardiac disease who were treated with clopidogrel at University Hospital in Lenven, Belgium.⁹ The average age at initiation of therapy was 4.9±4.1 years. Treatment was started with a dose of 0.5 to 1 mg/kg/day, but after minor bleeding (epistaxis and bruising) in many of the initial patients, the starting dose was lowered to 0.2-0.3 mg/kg/day. The average dose during treatment was 0.41±0.15 mg/kg/day. Forty-three patients also received aspirin, and two received warfarin as well. No thrombotic events were identified. Two patients who treated with clopidogrel and warfarin developed gastrointestinal bleeding.

In 2009, Maltz and colleagues reported their experience with clopidogrel at the Children's Hospital in Boston. Ninety patients were treated between March 2002 and August 2005, with a median age at initiation of 6.7 years (range 11 days to 17.9 years). Eighty-six patients were treated for cardiac indications, including 20 with a conduit or Blalock-Taussig shunt and 22 with an intravascular device or pacemaker. Four patients received clopidogrel after a stroke. Clopidogrel loading doses were used in only 21% of the children. The median starting dose was 1.3 mg/kg/day, with a range of 0.2-8.9 mg/kg/day. Doses were rounded to the nearest quarter tablet and given daily or every other day. Concomitant antiplatelet or anticoagulant therapy was common, with 58.9% of children receiving aspirin, 8.9% receiving warfarin, 14.4% receiving heparin, and 2.2% receiving a low-molecular-weight heparin. The median length of therapy was 44.5 days. Four patients (4.4%) had a significant bleeding event, and only one patient had a thrombotic event.

In addition to these papers, clopidogrel use has also been described in children with ventricular assist devices (VAD).^{11,12} In a report of eight children (4 to 55 months of age) with a Berlin Heart EXCOR pediatric VAD, patients were given an anticoagulant (heparin or warfarin) and antiplatelet therapy (aspirin with either clopidogrel or dipyridamole).¹¹ In spite of close monitoring of coagulation status and the degree of platelet inhibition, two patients developed

cerebral embolism (including one patient with visceral and renal thrombosis) and two had cerebral hemorrhage.

Clopidogrel was also used to prevent pump thrombus formation in a case report of a 15 year old with a DeBakey VAD Child device.¹² After repeated episodes of pump thrombosis during treatment with either heparin or warfarin, the patient was switched to a regimen of warfarin and clopidogrel, using a 150 mg loading dose followed by a dose of 75 mg/day. The patient continued on the warfarin and clopidogrel combination for another month without thrombotic or hemorrhagic complications. He was transplanted 84 days after VAD placement.

Contraindications

Clopidogrel is contraindicated in patients with active bleeding, including peptic ulcers. It is also contraindicated in patients with a previous hypersensitivity reaction to clopidogrel or any other component of the tablet.^{1,2}

Adverse Effects

The most frequently reported adverse effects with clopidogrel during premarketing clinical trials in adults include headache (7.6%), arthralgias (6.3%), dizziness (6.2%), back pain (5.8%), bruising (5.3%), rash (4.2%), edema or hypertension (4%), abdominal pain, nausea, or diarrhea (3-6%), and symptoms of an upper respiratory tract infection or influenza (7-9%). All values were equivalent to rates reported in patients receiving aspirin. Gastrointestinal hemorrhage and intracranial hemorrhage occurred in approximately 2-3% and 0.4-0.6% of patients, similar to rates with aspirin.^{1,2}

Thrombotic thrombocytopenic purpura has been reported in patients taking clopidogrel, with some cases resulting in patient death. This rare adverse reaction may occur at any point during therapy and requires urgent treatment, often using plasmapheresis.^{1,2}

Drug Interactions

Concomitant administration of clopidogrel with drugs that inhibit the activity of CYP2C19 may result in lower concentrations of the thiol metabolite and reduce efficacy. Administration of omeprazole has been shown to reduce clopidogrel metabolite concentrations by 40% and reduce inhibition of platelet aggregation by 30-50%. On the basis of these studies, the FDA mandated an update to the labeling for clopidogrel recommending that concomitant use of drugs known to inhibit CYP2C19 (including omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine) should be avoided.¹⁻³

At high doses, typically above those used in clinical practice, clopidogrel inhibits CYP2C9 and can reduce the metabolism of fluvastatin, phenytoin, tamoxifen, tolbutamide, toremide, warfarin, and some non-steroidal anti-inflammatory agents (NSAIDs). There is currently limited information on the clinical significance of these drug interactions. Clopidogrel may also increase concentrations of bupropion. Macrolide antibiotics may decrease the efficacy of clopidogrel, while rifamycins may increase clopidogrel's antiplatelet effect.^{1,2}

Administration of clopidogrel with other drugs affecting bleeding should be done with caution. Use of NSAIDs may increase the risk for gastrointestinal bleeding. While at usual doses, administration of clopidogrel in patients taking warfarin does not alter its pharmacokinetics, the risk for bleeding may be increased due to their combined effects on hemostasis.^{1,2}

Dosing Recommendations

The recommended dose of clopidogrel in adults is a single 300 mg oral loading dose followed by 75 mg given once daily. Combination therapy with aspirin is recommended in adults with acute coronary syndrome. Although not well studied, it has been suggested that CYP2C19 poor metabolizers should be given a higher dosing regimen, with a 600 mg loading dose and maintenance therapy of 150 mg once daily. Based on results from the PICOLO trial, infants and children up to 2 years of age should start therapy at 0.2 mg/kg/day. Dosing in older children is less well established; current studies suggest that a dose of 0.2 to 1 mg/kg/day may be an appropriate starting point. Clopidogrel may be taken with or without food.^{1,2}

Availability and Cost

Clopidogrel (Plavix[®]) is available in 75 and 300 mg tablets.^{1,2} The average wholesale price is \$159.77 for 30 of the 75 mg tablets and \$639.17 for 30 of the 300 mg tablets.¹³ Skillman and colleagues have recently published a stability study of an extemporaneously compounded clopidogrel oral suspension.¹⁴ The 5 mg/mL suspension was stable for up to 60 days at room temperature or under refrigeration.

Summary

Clopidogrel provides an alternative to aspirin for inhibition of platelet aggregation in pediatric patients at risk for venous thrombosis. Several studies, including the PICOLO trial, have provided preliminary data supporting its safety and efficacy in the pediatric population. Prescribers should be aware of new information on the impact of differences in metabolic function on efficacy, as well as drug interactions, when initiating therapy.

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Formulary Update

The Pharmacy and Therapeutics Committee did not meet in April. Their next meeting will be on 5/28/10.

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