Dosing of Clopidogrel for Platelet Inhibition in Infants and Young Children

Primary Results of the Platelet Inhibition in Children On cLOpidogrel (PICOLO) Trial

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Background—Infants and young children with certain types of heart disease are at increased risk for thromboses. Clopidogrel 75 mg/d is used in adults to prevent thrombotic events. The dose to achieve similar platelet inhibition in children is unknown. The objectives of the present study were (1) to determine the dose of clopidogrel needed in infants and young children to achieve a mean 30% to 50% inhibition of 5-μmol/L ADP–induced platelet aggregation (ie, inhibition similar to that observed with 75 mg in adults) and (2) to assess the safety and tolerability of clopidogrel in infants and young children.

Methods and Results—We performed a prospective, multicenter, randomized, placebo-controlled trial evaluating the pharmacodynamics of clopidogrel in children (0 to 24 months) with a cardiac condition at risk for arterial thrombosis. Patients were randomized to clopidogrel versus placebo in a 3:1 ratio in 4 sequential groups (0.01, 0.10, 0.20, and 0.15 mg/kg) for ≥7 and ≤28 days. Platelet aggregation was assessed at baseline and steady state by light-transmission aggregometry. Of 116 patients enrolled, 92 (50% neonates, 50% infants/toddlers) were randomized, and 73 completed the study. A total of 79% of the randomized and treated patients were taking aspirin. Compared with placebo, clopidogrel 0.20 mg · kg⁻¹ · d⁻¹ resulted in a mean 49.3% (95% confidence interval 25.7% to 72.8%) inhibition of the maximum extent of platelet aggregation and a mean 43.9% (95% confidence interval 18.6% to 69.2%) inhibition of the rate of platelet aggregation. There was marked interpatient variability in the degree of platelet aggregation inhibition within each treatment-dose group and age group. No serious bleeding events occurred.

Conclusions—Clopidogrel 0.20 mg · kg⁻¹ · d⁻¹ in children 0 to 24 months of age achieves a platelet inhibition level similar to that in adults taking 75 mg/d. Clopidogrel is well tolerated in infants and young children at this dose. (Circulation. 2008;117:553-559.)

Key Words: thrombosis • clopidogrel • pediatrics • antiplatelet agents • platelet aggregation • dosing

Antiplatelet therapy has established benefits in adult patients with unstable angina, cerebrovascular disease, and peripheral arterial disease.¹,² Infants and young children with certain types of heart disease (including those with single ventricle after palliation with a systemic-to–pulmonary artery shunt, Kawasaki disease, and intracardiac stents or devices) are likewise at risk for thrombotic events, including shunt thrombosis, coronary artery thrombosis, and thromboembolic arterial stroke.³ Although aspirin (ASA) is often used in children with these conditions, ASA alone in many instances may not be sufficient to prevent arterial thrombosis, because it inhibits only 1 pathway of platelet activation, the cyclooxygenase pathway.³

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Clopidogrel, a thienopyridine derivative, produces its antiplatelet effect through an active metabolite that specifically
and irreversibly modifies the ADP purinergic P2Y<sub>12</sub> platelet receptor and through the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex, thereby inhibiting platelet aggregation.<sup>6,9</sup> This pathway provides an antplatelet effect that is additive to the inhibition of the cyclooxygenase pathway by ASA. Clinical trial evidence supports the use of clopidogrel at a maintenance dose of 75 mg/d in adults for treatment and prevention of major cardiac events across a wide range of high-risk patients.<sup>7–10</sup> Clopidogrel doses of 75 mg/d in adults typically achieve a mean 30% to 50% inhibition of 5-μmol/L ADP–induced platelet aggregation.<sup>11–15</sup> Although the appropriate doses of antiplatelet drugs in children are known to differ from adults,<sup>16</sup> the appropriate dose of clopidogrel in children is unknown. In the present study, we therefore sought to determine in infants and young children (aged ≤24 months) at risk for arterial thrombosis the appropriate dose of clopidogrel that would achieve similar levels of ADP-induced platelet aggregation as 75 mg in adults. This age group was selected as the focus of the study because it reflects a high-risk population of infants and young children with recently palliated congenital heart disease who may potentially benefit from the therapeutic effects of clopidogrel.<sup>17</sup>

**Methods**

The Platelet Inhibition in Children On clopidogrel (PICOLO) trial was a prospective, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study to determine the dose of clopidogrel by pharmacodynamic assessment to achieve a mean 30% to 50% inhibition of 5-μmol/L ADP–induced platelet aggregation in neonates or infants/toddlers with a systemic-to–pulmonary artery shunt or another cardiac condition with a risk for arterial thrombosis, including a stent placement. A secondary objective of the study was to assess the safety of clopidogrel in this population. Patients were recruited from 22 centers in Belgium, Canada, France, Germany, Italy, and the United States (see Appendix in the Data Supplement). The trial was approved by the institutional review board of each participating institution, as well as the appropriate national ethics committee. Written informed consent for trial participation was obtained from the parent or guardian of each patient. The trial was planned by the Steering Committee; an independent Platelet Aggregation Committee reviewed the pharmacodynamic data, and an independent Data Safety Monitoring Board (DSMB) monitored the conduct of the trial. The Vascular Biology Center of Excellence, University of Tennessee Health Science Center provided central core laboratory interpretation of the platelet aggregation tracings. To ensure standardization and quality of the platelet measures, all sites were trained and required to demonstrate appropriate sample handling and equipment use before participation in the study. The anticoagulants and agonists used for the platelet aggregation studies were supplied by the core laboratory to each site after they were quality tested for response and activity before shipment. The Duke Clinical Research Institute performed the data collection, entry, and analysis. Funding for the PICOLO trial was provided by sanofi-aventis and Bristol-Myers Squibb. The sponsors had nonvoting input in the Steering Committee and were responsible for auditing at individual study sites. The Steering Committee bears full responsibility for the analysis of the results and the preparation of the manuscript.

**Patients**

Patients were eligible for enrollment in the study if they were 0 to 24 months of age with congenital heart disease palliated with a systemic-to-pulmonary artery shunt or another cardiac condition with a risk of arterial thrombosis (eg, Kawasaki disease or intravascular or intracardiac stent). Patients were excluded from the study if they weighed <2 kg; were <35 weeks’ gestational age; were receiving or planned to undergo treatment with oral or intravenous anticoagulant medications (although ASA was permitted, as was periprocedural heparin); had ongoing bleeding, risk of bleeding (eg, history of hemophilia, von Willebrand disease, or other known hemorrhagic disorder), previous intracranial hemorrhage, or platelet count <80,000 per mm<sup>3</sup>; had received a platelet transfusion within the previous 7 days; or had experienced hepatic or renal failure. ASA use was permitted during participation in the study per the investigator’s discretion; however, the patient had to be taking the same stable dose of ASA throughout the study (ie, during the baseline assessment and until the steady state platelet aggregation assessment of the study drug).

**Trial Procedures**

After written informed consent was obtained from the parent or guardian, patients were randomly assigned to clopidogrel versus placebo in a 3:1 ratio in 4 sequential groups (0.01, 0.10, 0.20, and 0.15 mg/kg) for at least 7 days of consecutive dosing within a 28-day period (>7 and <28 days). Patients were also stratified by age: neonates ≤30 days old and infant/toddlers >30 days to 24 months old. Study-drug assignment was performed centrally by an interactive voice-response system on the basis of a preestablished randomization scheme stratified according to age group. If a patient did not undergo a steady state platelet aggregation assessment, the next available patient who met the study criteria and gave consent was enrolled. The investigators were aware of the treatment cohort dose level but were unaware of whether the patient was to receive placebo or active drug. Study drug was supplied as clopidogrel powder or placebo (mannitol powder) to be reconstituted in a solvent to a 5-mg/mL solution. Additional dilutions were achieved by 1:9- and 1:99-mL dilutions of the original solutions; patients were dosed a volume according to their weight, with a once-daily dose of 0.01, 0.1, 0.15, or 0.2 mg/kg provided. Compliance was assessed by daily dosing logs, and data on adverse events were collected throughout the time of study-drug treatment and until 1 month thereafter. The severity of any bleeding event was judged by the principal investigator and was deemed a serious hemorrhage if the bleeding event was associated with hemodynamic compromise or was life-threatening; required transfusion; led to death, prolongation of hospitalization, or significant disability; or was judged to be otherwise medically important. The DSMB received periodic summaries of all adverse events, serious or not, and reviewed adverse event severity classifications assigned by the principal investigator. The DSMB chairperson received narratives of the serious adverse events as they occurred. The Steering Committee reviewed all serious adverse events after evaluation by the DSMB. Platelet aggregation was assessed at baseline and steady state (>7 and ≤28 days of treatment) by light-transmission aggregometry. Pharmacodynamic efficacy (degree of platelet aggregation inhibition at baseline and steady state) was determined by light-transmission aggregometry with 3.2% sodium citrate as an anticoagulant and 5 μmol/L of ADP as the agonist. Light-transmission aggregometry was performed as described previously,<sup>18</sup> and the percentage inhibitions of (1) the maximal extent of platelet aggregation and (2) the rate of aggregation were calculated. The platelet aggregation studies were run in duplicate for each patient. Both tracings were sent to the Vascular Biology Center of Excellence, University of Tennessee Health Science Center, which provided central core laboratory interpretation of the platelet aggregation tracings. Routine laboratory assessment of complete blood count and chemistries were obtained before study drug administration and at the end of treatment.

The first dose group was 0.01 mg/kg. After platelet-inhibition assessments had been completed on a minimum of 3 active patients and 1 placebo patient per age group, the independent Platelet Aggregation Committee and DSMB met separately to assess the data and advise whether to move to the next dosing group. The Platelet Aggregation Committee assessed whether the goal of a mean 30% to 50% inhibition of 5-μmol/L ADP–induced platelet aggregation had been achieved. The DSMB assessed the pharmacodynamic data and any potential adverse events and bleeding. If there were no serious
adverse events, including serious bleeding, and the target goal of platelet inhibition had not been achieved, the DSMB voted whether to continue to enroll patients in the same dose or proceed to enroll patients into the next dosing stratum. Subsequent changes in dosing to 0.1 and 0.2 mg/kg proceeded in a similar manner. The dose of 0.15 mg/kg in neonates was recommended for testing by the committees only after completion of the 0.2-mg/kg dose group.

Statistical Analysis

Because this was the first planned clinical study of the use of clopidogrel in infants, there were no specific reference data on which to base the sample size. Based on previous experience with adult pharmacological and pharmacokinetic assessments, a sample size of 12 subjects (9 clopidogrel and 3 placebo) per dose level and age category was chosen. With a conservative estimate of 50±30% (mean±SD) inhibition of maximum aggregation intensity11–15 and with the assumption of no effect in placebo patients, 9 patients per group would provide 90% power to detect a difference from placebo at the 5% significance level (2-sided).

All randomized patients who received study drug were assessed for safety. Only randomized patients who had a baseline (pretreatment) and a steady state (at least 7 consecutive days of treatment) assessment of platelet aggregation were included in the analysis of pharmacodynamic parameters. Data from the placebo groups were pooled. To assess primary outcomes, ANOVA was performed on percent inhibition of maximum extent of aggregation and percent inhibition of rate of aggregation separately with model terms for treatment group, age group, and the treatment group–by–age group interaction. The differences between active-dose level and placebo were estimated within the ANOVA framework with 95% confidence intervals. All hypothesis tests were performed with 2-sided tests at the 5% significance level. Demographic/baseline characteristics and safety results are summarized with the population of all randomized and treated patients. Results are summarized by treatment (each clopidogrel dose and pooled placebo results) and age group (neonates and infants/toddlers).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study Population

Of 339 eligible patients, 116 were enrolled; the main reason for failure to enroll eligible patients was that the parents did not provide consent for the study. Of the 116 enrolled patients, 24 were not randomized because they either became ineligible for the study owing to a change in their clinical status or their parents withdrew consent. A total of 92 patients were therefore randomized (46 neonates, 46 infants/toddlers). Six of these patients who were randomized but not treated did not have evaluable baseline assessments and were therefore replaced. The treated patients did not differ significantly in age or cardiac diagnosis from the patients who were eligible for the study. Seventy-three patients (34 neonates, 39 infant/toddlers) completed the dosing regimen and had interpretable baseline and steady state platelet aggregation assessments. A total of 10 patients discontinued the study drug (3 owing to an adverse event, 2 because of bleeding, 1 owing to death; see Figure 1 for remaining reasons). Three patients completed the study and could not be evaluated for the following reasons: nonevaluable platelet aggregation assessment, baseline platelet aggregation assessment with <20% platelet response to 5 μmol/L ADP, and withdrawal of informed consent (Figure 1).

Of the randomized and treated patients, 84.9% were white, 5.8% were black, 11.6% were of Hispanic/Latino ethnicity, and 37.2% were female (Table 1). The most common cardiac diagnoses were as follows: hypoplastic left heart syndrome in 33.7%, pulmonary atresia with intact ventricular septum in 15.1%, tricuspid atresia in 9.3%, tetralogy of Fallot in 8.1%, double-inlet left ventricle in 7.0%, and double-outlet right ventricle in 4.7%. A total of 73.3% of the patients had undergone placement of a systemic-to–pulmonary artery shunt, 24.4% had an intracardiac or intravascular stent placed,

![Figure 1. Trial flow diagram. *Completed dosing regimen and had both interpretable baseline and steady state platelet aggregation assessment.](http://circ.ahajournals.org/)}
1.2% had Kawasaki disease, and the remaining patients had an arterial graft in place. Seventy-nine percent were taking ASA/81 mg/d; the mean dose of ASA was 8.8/14.0 mg · kg/1·d/1 with a dosing range of 1.3 to 87.6 mg · kg/1·d/1.

**Dose Response**

Figure 2A shows the mean (±SD) percent inhibition of the maximum extent of platelet aggregation in response to 5 μmol/L ADP for placebo and each clopidogrel dose level; Figure 2B shows the mean (±SD) percent inhibition of the rate of platelet aggregation in response to 5 μmol/L ADP for placebo and each clopidogrel dose level.

Table 2 demonstrates the active drug versus placebo estimates and 95% confidence intervals for the percent inhibition of the maximum extent of platelet aggregation and the percent inhibition of the rate of platelet aggregation according to age group and dose. Evaluation of the interaction between age group and dose did not reveal any significant interaction for either inhibition of maximum extent of platelet aggregation ($P=0.80$) or inhibition of rate of aggregation ($P=0.76$). Unadjusted pairwise comparisons of the active-dose groups yielded significant results for both aggregation parameters (inhibition of maximum extent and inhibition of rate of aggregation) when we compared 0.01 versus 0.2 mg/kg ($P=0.0001$ and $P=0.0328$) and 0.1 versus 0.2 mg/kg ($P=0.0078$ and $P=0.0077$), respectively. These data indicate that the 0.20-mg/kg dose achieved the target mean 30% to 50% inhibition of 5-μmol/L ADP–induced platelet aggregation for both the maximum extent and the rate of platelet aggregation.

**Safety**

Eight treatment-emergent serious adverse events occurred in 6 patients during the course of the study (3 serious adverse events in patients receiving placebo and 5 in patients receiving active clopidogrel). In the placebo group, 1 case each of increasing congestive heart failure, sepsis, and shunt thrombosis was reported. In the clopidogrel treatment group, oxygen desaturation (at 0.15 and 0.20 mg/kg), decrease in platelet count (at 0.01 mg/kg), bradycardia (at 0.15 mg/kg), and hypotension (at 0.15 mg/kg) were reported. Only the decrease in platelet count was considered “possibly related”
to study treatment by the investigator. There were no serious hemorrhagic adverse events during the study. Two patients in the placebo group and 2 in the clopidogrel group (at 0.01 and 0.2 mg/kg) experienced minor bleeding (eg, blood in stool with no change in hematocrit or hemoglobin level). The patient (at 0.15 mg/kg) who experienced both bradycardia and hypotension after receiving 4 doses of the study drug died after experiencing these events. The death was judged by the site investigator as unrelated to the study drug.

Discussion

Although antiplatelet therapy has been studied extensively in adult cardiovascular and cerebrovascular disease, evidence for the benefit of antiplatelet therapy in young children is limited. Furthermore, the appropriate dose of clopidogrel in children is unknown. We recently completed an observational study evaluating the clinical outcomes of palliative surgery that included a systemic-to-pulmonary artery shunt in infants and young children with cyanotic congenital heart disease. The study showed that ASA appeared to lower the risk of death and shunt thrombosis in this patient population. We therefore undertook the present study to evaluate an appropriate dose of clopidogrel in this patient population, which has a therapeutic need for antiplatelet therapy.

Compared with the presently reported dose of 0.2 mg/kg, previous reports of clopidogrel use in children have used substantially higher doses based on extrapolation (in mg/kg) from adult dosing. Finkelstein et al performed a retrospective review of 15 infants and children with a median age of 3.5 years receiving clopidogrel 1 to 6 mg · kg⁻¹ · d⁻¹. One child had a massive upper gastrointestinal bleed while undergoing triple-antithrombotic therapy. Soman et al reported a prospective study of 17 children with a mean age of 8.8 years with arterial ischemic stroke who received clopidogrel at a dose of 1 mg · kg⁻¹ · d⁻¹. Two of these children developed subdural hematomas while taking this dose in conjunction with ASA.

Because of safety considerations, it is important to conduct proper pharmacodynamic and dosing studies in children. A recent study conducted by investigators at the US Food and Drug Administration demonstrated that in 21% of pediatric dosing studies, important new information led to new dosing recommendations. Extrapolated dosing based on adult studies fails to take into account the developmental and physiological differences in drug metabolism and effects in children.

### Table 2. Inhibition of ADP-Induced Platelet Aggregation: Active Clopidogrel Dose Level Versus Placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Difference Estimates (95% Confidence Intervals)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0.01 mg/kg vs Placebo</td>
</tr>
<tr>
<td>% Inhibition of maximum extent of aggregation</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>−12.28 (−44.16 to 19.59)</td>
</tr>
<tr>
<td>Neonates</td>
<td>−2.37 (−53.95 to 49.21)</td>
</tr>
<tr>
<td>Infants</td>
<td>−17.80 (−59.49 to 23.89)</td>
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<tr>
<td>% Inhibition of rate of aggregation</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>8.80 (−25.47 to 43.07)</td>
</tr>
<tr>
<td>Neonates</td>
<td>9.77 (−45.61 to 65.15)</td>
</tr>
<tr>
<td>Infants</td>
<td>8.02 (−36.75 to 52.78)</td>
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</tbody>
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The present data demonstrate that infants and young children require a considerably lower dose of clopidogrel per kilogram of body weight than do adults to achieve 30% to 50% inhibition of 5-μmol/L ADP–induced platelet aggregation, ie, the level of inhibition achieved with the approved adult dose. In addition, the present data show that there is variability in the percent inhibition of platelet aggregation with clopidogrel. The SD for percent inhibition of the maximum extent of aggregation was 37.4%, derived from the pooled variance of the ANOVA model. This finding is consistent with the known variability in response to clopidogrel in the adult population.15,22,23

Why do young children require a lower dose of clopidogrel per kilogram of body weight than adults? The platelets of newborns and children do not differ significantly from those of adults in number or structure.24 Platelets from neonates demonstrate enhanced adhesion compared with adult platelets owing to the presence in neonatal plasma of larger, more functionally potent von Willebrand factor multimers. These multimers may result from decreased activity of von Willebrand factor–cleaving protease in neonatal plasma.24 However, platelets from neonates, compared with platelets of adults and children, have a decreased response to standard, physiologically relevant agonists.3 This hyporesponsiveness is reflected in decreased aggregation, decreased granule secretion, and decreased expression of activation markers when platelets are stimulated in vitro with ADP, collagen, epinephrine, thromboxane analogues, or low-dose thrombin.3,25 These differences in platelet activation have been shown to be at least in part the result of impaired receptor-mediated signal transduction in thromboxane synthesis, G-protein–mediated response, and intracellular calcium mobilization.3 26 This ADP-induced hyporeactivity in the platelets of young children compared with adults3,25 may be part of the explanation for the ability of a lower clopidogrel dose per kilogram to achieve comparable inhibition of platelet aggregation compared with adults. Additional possible factors in this regard that have not yet been investigated include potential differences between young children and adults in clopidogrel absorption, clopidogrel metabolism through cytochrome P450, and the number of P2Y12 receptors per platelet.

The present study has some limitations. First, although the present study is one of the very few randomized, controlled trials in the field of pediatric arterial thrombosis,16 this was a relatively small study in terms of the number of patients with evaluable platelet aggregation data in each dose group. Therefore, the study groups cannot be compared with regard to age, ethnicity, and diagnoses. In addition, we did not test or control for period effects, which are a possibility in a study with a sequential randomization protocol; however, because the present study was conducted over a relatively short time frame, the impact of a period effect is likely to be minimal. Our evaluable cohort was not strictly an intent-to-treat population, because patients who discontinued the study did not have a follow-up platelet aggregation assessment, and there is no way to establish that aggregability in these patients would have been comparable to that in the cohort that completed the study. Also, we could not perform platelet function tests other than ADP-induced platelet aggregation during the present study because this would have required a prohibitively large amount of additional blood to be drawn from these small infants and young children. Lastly, in adults taking clopidogrel, a ceiling effect is noted at ≈50% to 60% of platelet inhibition.27 This level of platelet inhibition was the planned target, so we did not test doses of clopidogrel >0.2 mg/kg (or define a dose at which a ceiling effect takes place in children). It is therefore unclear whether even higher doses would increase the degree of platelet inhibition in this patient population.

Conclusions

The present study demonstrates that clopidogrel doses of 0.20 mg · kg⁻¹ · d⁻¹ in infants and young children 0 to 24 months of age with a systemic-to-pulmonary artery shunt or stent achieve platelet inhibition levels similar to those in adults taking the standard adult dose of clopidogrel 75 mg/d. Thus, infants and young children require a considerably lower clopidogrel dose per kilogram of body weight than adults. Unlike previous reports of higher doses of clopidogrel in children,19,20 clopidogrel 0.2 mg/kg was well tolerated in the present pediatric population, with infrequent adverse events that were rarely attributed to the study drug. Results presented here are restricted to the study population and may not be extrapolated to all children with thrombotic disease. Additional studies might determine responsiveness to clopidogrel in different age groups and with specific disease subtypes, but it may be difficult to recruit sufficient numbers of children in certain specific disease subgroups. The upcoming Clopidogrel to Lower Arterial thrombotic Risk In NEonates and infants Trial (CLARINET) is a multicenter, randomized, controlled trial that will assess efficacy and safety of the presently established dose of clopidogrel 0.2 mg · kg⁻¹ · d⁻¹ in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to–pulmonary artery shunt.

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Disclosures

Drs Bokesch, Graham, Takahashi, and Sanders served on the Steering Committee and received honoraria from sanofi-aventis. All authors indicate that their institutions have received research grants from Bristol-Myers Squibb and sanofi-aventis.

References


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