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Platelet Activity Associated with Concomitant Use of Clopidogrel and Proton Pump Inhibitors in Children with Cardiovascular Disease

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Abstract

Context—In adults with acute coronary syndrome, decreased platelet inhibition associated with concomitant use of clopidogrel and proton pump inhibitors (PPI) has been reported.

Objective—To evaluate platelet activity associated with PPI + clopidogrel vs. clopidogrel alone in children enrolled in the Platelet Inhibition in Children On cLOpidogrel (PICOLO) trial of clopidogrel in children with a cardiac condition at risk for arterial thrombosis.

Design—Patients 0–24 m randomized to active therapy in the PICOLO trial were included in the present analysis. Platelet aggregation inhibition at baseline and steady state were evaluated in patients taking clopidogrel + PPI vs. clopidogrel only in the overall cohort and sub-group of clopidogrel responders.

Results—A total of 49 patients were included (44 clopidogrel only, five clopidogrel + PPI); median age 38 days (interquartile range [IQR] 17–157 days). The majority of patients in each group had undergone systemic-to-pulmonary artery shunt. Compared with the clopidogrel group, patients in the clopidogrel + PPI group had a trend toward lower percent inhibition of maximum extent of platelet aggregation overall (median 6%, IQR 0–44% vs. 49%, IQR 19–63%, $P = 0.09$), and a significant reduction in the clopidogrel responders sub-group (median 25%, IQR 3–45% vs. 53%, IQR 38–65%, $P = 0.04$). There was no difference in percent inhibition of rate of platelet aggregation.

Conclusions—Concomitant use of PPI + clopidogrel may be associated with decreased platelet inhibition in children with cardiac disease. Further study in a larger population and assessment of associated clinical outcomes is warranted.

Keywords

Congenital Heart Disease; Thrombosis; Antiplatelet Agents

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Conflict of interest: None.

Introduction

Recent studies in adults with acute coronary syndrome have reported that concomitant use of clopidogrel and proton pump inhibitors (PPI) may be associated with an attenuation of the platelet inhibitory effects of clopidogrel.^{1,2} This has been attributed to competitive inhibition by PPIs of a cytochrome P450 isoenzyme involved in the metabolism of clopidogrel, such that the inhibitory effects of clopidogrel on platelet activation are reduced.^{1,2} It remains controversial whether this adversely impacts clinical outcomes in this population.^{3–5}

Clopidogrel may also be considered in the treatment of infants and children with certain types of cardiac disease at increased risk for arterial thrombosis (e.g., patients with single ventricle after palliation with systemic-to-pulmonary artery shunt, Kawasaki disease, or intravascular stents).⁶ Gastroesophageal reflux occurs frequently in children with cardiac disease and treatment with PPIs and other anti-reflux medications is common.⁷ The impact of concomitant treatment with a PPI on platelet activity in children with cardiovascular disease taking clopidogrel has not been examined to date. The purpose of this analysis was to evaluate platelet activity associated with concomitant PPI therapy in children with cardiovascular disease enrolled in the Platelet Inhibition in Children On cLO-pidogrel (PICOLO) trial.

Methods

Study Design and Data Collection

The PICOLO trial was a prospective, multi-center, randomized, double-blind, placebo-controlled, dose-ranging trial of clopidogrel in children with a cardiac condition at risk for arterial thrombosis.⁶ Trial procedures and primary results have been previously published (clinicaltrials.gov, number NCT00115375).⁶ Briefly, patients 0–24 months of age with congenital heart disease palliated with a systemic-to-pulmonary artery shunt or another cardiac condition at risk for arterial thrombosis (Kawasaki disease or intravascular stent) were eligible for inclusion. Patients who weighed <2 kg or were <35 weeks gestational age were excluded, along with those who were: (1) undergoing treatment with other anticoagulant medications (aspirin and peri-procedural heparin were permitted); (2) had a history of bleeding or a condition with increased bleeding risk; and (3) had renal or hepatic failure. Patients were randomly assigned to clopidogrel versus placebo in a 3:1 ratio with 4 sequential dose 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. Platelet aggregation was assessed at baseline and steady state (≥ 7 and ≤ 28 days of treatment). The 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 μ mol/L adenosine diphosphate (ADP) as the agonist. Light-transmission aggregometry was performed as described previously and the percent inhibition of the maximal extent of platelet aggregation and the rate of aggregation were assessed by a central core laboratory.^{6,8} A total of 73 patients were randomized, completed the study, and had interpretable baseline and steady state platelet aggregation assessments. Of these, 49 patients were on active therapy and included in the present analysis.

Analysis

Data were described using standard summary statistics. Platelet aggregation was evaluated in patients on concomitant PPI therapy at enrolment vs. those taking clopidogrel alone. Data from all dose groups greater than 0.01 mg/kg were pooled for analysis. The percent inhibition of the rate of platelet aggregation and percent inhibition of the maximum extent of platelet aggregation in the clopidogrel + PPI vs. clopidogrel only groups were compared

using the Wilcoxon Rank Sum test. Analyses were performed both overall, and in the sub-group of clopidogrel responders (those with any measurable inhibition of platelet aggregation).⁹ All analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC). A *P* value <0.05 was considered statistically significant.

Results

A total of 49 patients were included: 44 clopidogrel only patients (22 neonates, 22 infants/toddlers) and five patients who received clopidogrel + PPI (two neonates, three infants/toddlers). The latter group consisted of four patients taking omeprazole and one patient taking lansoprazole. Study population characteristics are displayed in Table 1.

Table 2 displays platelet activity data in the clopidogrel only and clopidogrel + PPI groups, both overall and in the sub-group of clopidogrel responders. There was a trend toward lower percent inhibition of the maximum extent of aggregation in the clopidogrel + PPI vs. clopidogrel only group in the overall cohort; this difference reached statistical significance in the clopidogrel responders sub-group. No significant differences were seen between groups in the percent inhibition of rate of aggregation.

Discussion

These data suggest that in children with a cardiac condition at risk for arterial thrombosis, those taking a PPI in addition to clopidogrel may have reduced inhibition of platelet aggregation compared with those on clopidogrel alone. Further evaluation is necessary to determine the clinical significance of this finding. In adults, the impact of PPI therapy in addition to clopidogrel on clinical outcomes remains unclear. Some studies have reported that concomitant use of a PPI with clopidogrel is associated with a reduction in the clinical benefit of clopidogrel. Ho et al. evaluated a cohort of 8205 patients with acute coronary syndrome and found that the use of a PPI in addition to clopidogrel was associated with an increased risk of death or re-hospitalization compared with the use of clopidogrel alone (adjusted odds ratio 1.25, 95% confidence interval 1.11–1.41).³ It is hypothesized that this is due to diminished platelet inhibitory activity of clopidogrel in patients taking concomitant PPI. In a randomized controlled trial, Gilard et al. showed that patients randomized to omeprazole plus clopidogrel vs. clopidogrel alone following coronary artery stent placement did not have as great a reduction in platelet reactivity index following 7 days of therapy (51.4% vs. 39.8%, *P* < 0.0001).² This has been attributed to competitive inhibition by PPIs of one of the cytochrome P450 enzymes involved in the activation of clopidogrel.^{1,2} However, other recent adult studies have suggested that the impact of PPI's on clinical outcomes in patients taking clopidogrel may not be as great, and may in part be due to methodologic issues such as inadequate adjustment for confounders in previous studies.⁵ In a recent meta-analysis of 23 studies involving 93 278 patients, analysis of propensity-matched or randomized trials only showed no statistically significant increase in acute coronary syndrome events associated with PPI and clopidogrel vs. clopidogrel alone (relative risk 1.15; 95% CI 0.89–1.48), whereas observational studies generally showed a significant association (relative risk 1.54; 95% CI 1.23–1.92).⁴ Thus, debate remains surrounding the impact of PPI on outcomes associated with clopidogrel in the adult literature.

Data from the present analysis suggest reduced levels of the maximum extent of aggregation, but not the rate of aggregation, in children with cardiovascular disease taking a PPI along with clopidogrel. The clinical implications of these findings are unclear. Given the increased emphasis on feeding, weight gain, and treatment of gastroesophageal reflux in children with congenital heart disease, treatment with anti-reflux medications including PPIs

in this population is becoming increasingly common.^{7,10} This is the first study to date to evaluate the interaction of treatment with PPI on other medical therapies used in these complex children.

The limitations of this analysis include small sample size, observational design, and lack of outcomes data. Evaluation of a larger population of children with cardiovascular disease may be indicated to further define the impact of PPI therapy on platelet inhibition and clinical outcomes associated with clopidogrel.

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Table 1
Patient Characteristics

Characteristic	Clopidogrel (n = 44)	Clopidogrel + PPI (n = 5)	Overall (n = 49)
Median age, days (IQR)			
Neonates	16 (14, 19)	21 (18, 24)	17 (14, 21)
Infants/Toddlers	157 (124, 270)	455 (84, 562)	157 (124, 271)
Sex, male (n, %)	26 (59)	4 (80)	30 (61)
Ethnicity (n, %)			
Hispanic/Latino	4 (9)	1 (20)	5 (10)
Race (n, %)			
White	38 (86)	3 (60)	41 (84)
Black	2 (5)	0 (0)	2 (4)
Asian	1 (2)	0 (0)	1 (2)
Native American	1 (2)	1 (20)	2 (4)
Other	2 (5)	1 (20)	3 (6)
Median weight, kg (IQR)			
Neonates	3.2 (3.0, 3.4)	3.7 (3.5, 3.8)	3.3 (3.0, 3.4)
Infants	5.8 (4.2, 7.2)	8.3 (3.5, 10.9)	5.9 (4.2, 7.3)
Cardiac Diagnoses (n, %)			
Hypoplastic left heart syndrome	11 (25)	3 (60)	14 (29)
Pulmonary atresia/intact ventricular septum	8 (18)	0 (0)	8 (16)
Tricuspid atresia	3 (6)	0 (0)	3 (6)
Tetralogy of Fallot	3 (6)	1 (20)	4 (8)
Double-inlet left ventricle	3 (6)	0 (0)	3 (6)
Double-outlet right ventricle	2 (4)	0 (0)	2 (4)
Asplenia with single ventricle	1 (2)	0 (0)	1 (2)
Polysplenia with single ventricle	0 (0)	0 (0)	0 (0)
Ebstein's anomaly	1 (2)	0 (0)	1 (2)
Kawasaki disease	0 (0)	0 (0)	0 (0)
Other	12 (27)	1 (20)	13 (27)
Procedures*			
Systemic-to-pulmonary artery shunt	29 (65)	4 (80)	33 (67)
Stent	15 (34)	2 (40)	17 (34)
Arterial graft	1 (2)	2 (40)	3 (6)

* Some patients with more than 1 procedure, may add up to more than 100%.

IQR, interquartile range.

Table 2

Platelet Activity

	Clopidogrel (n = 44)	Clopidogrel + PPI (n = 5)	P value
Percent inhibition of maximum extent of aggregation			
Overall	49% (19–63)	6% (0–44)	0.09
Clopidogrel responders	53% (38–65)	25% (3–45)	0.04
Percent inhibition of rate of aggregation			
Overall	33% (–1–53)	19% (12–21)	0.40
Clopidogrel responders	45% (27–59)	20% (16–33)	0.11

Data are displayed as median and interquartile range.