The Safety and Efficacy of Clopidogrel in Children with Heart Disease: A Systematic Review

Kristen Schmiedeskamp

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The Safety and Efficacy of Clopidogrel in Children with Heart Disease: A Systematic Review

Abstract

Background: Clopidogrel, an oral antiplatelet, has been used off-label in pediatric patients at risk for thrombosis, including those with heart disease, for more than a decade. While numerous clinical trials in adults have resulted in the formation of comprehensive management guidelines, considerably less is known about the safety and efficacy of clopidogrel use in children.

Method: An exhaustive literature search was performed using PubMed, Web of Science, Cochrane, Medline, CINAHL and International Pharmaceutical Abstracts. The keywords searched included “clopidogrel”, “child”, “teen”, “young”, “pediatric”, “boy”, “girl”, “adolescent” and “heart diseases” individually and in combination. The search was limited to the English language and articles older than ten years were excluded. After eliminating duplicate articles and those irrelevant to the topic of interest, seven studies were identified for review and three were selected.

Results: Three studies were reviewed, two of which were retrospective chart reviews and one randomized control trial. These studies included children with congenital or acquired heart disease, ages 8 days to 18 years old. Doses varied by study from 0.01 mg/kg/day to 6 mg/kg/day. Very few thrombotic events occurred and these events were rarely attributed to clopidogrel. The most frequent complication was skin bruising and minor bleeding.

Conclusion: Clopidogrel appears to be relatively well tolerated in infants and children at low doses, but should be used cautiously, particularly when administered in combination with other antiplatelet or anticoagulants, as it may increase bleeding risks.

Keywords: Clopidogrel, Heart Diseases, Child and Pediatric

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The Safety and Efficacy of Clopidogrel in Children with Heart Disease:

A Systematic Review

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Biography

Kristen Schmiedeskamp is a native Oregonian. She majored in Biology and Psychology and also played Division I Lacrosse while at Saint Mary's College of California. After completion of her undergraduate degree, she moved home to Portland, where she worked in Inpatient Neurology Rehabilitation for three years. Before beginning the Physician Assistant Program at Pacific University, Kristen spent time as a Clinical Research Coordinator for a local health system.

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ABSTRACT

Background: Clopidogrel, an oral antiplatelet, has been used off-label in pediatric patients at risk for thrombosis, including those with heart disease, for more than a decade. While numerous clinical trials in adults have resulted in the formation of comprehensive management guidelines, considerably less is known about the safety and efficacy of clopidogrel use in children.

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Results: Three studies were reviewed, two of which were retrospective chart reviews and one randomized control trial. These studies included children with congenital or acquired heart disease, ages 8 days to 18 years old. Doses varied by study from 0.01 mg/kg/day to 6 mg/kg/day. Very few thrombotic events occurred and these events were rarely attributed to clopidogrel. The most frequent complication was skin bruising and minor bleeding.

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INTRODUCTION

Background

First approved by the Food and Drug Administration in 1997 for the prevention of thrombosis in adults with acute coronary syndrome, recent ischemic stroke, myocardial infarction or peripheral arterial disease, clopidogrel, a thienopyridine derivative, has been used off-label in pediatric patients for more than a decade. Clopidogrel is a potent oral agent that once metabolized to its active “thiol” metabolite, works by irreversibly inhibiting platelet aggregation. Whether used in children or adults, it is frequently prescribed in conjunction with other agents such as aspirin (ASA), with the intent of targeting multiple platelet activation pathways to aid in better prevention of thrombosis (Buck, 2010).

Antiplatelet therapy is commonly used in children with certain forms of congenital heart or acquired heart disease, who are predisposed to thrombotic vascular complications, or to those who have suffered an ischemic stroke (Israels and Michelson, 2006). Cardiac catheterization or device implantation further increase the risk of thrombus formation, as described in one study of 4592 pediatric catheterizations at The Hospital for Sick Children in Toronto, which reported 3.8% rate of vascular complications with arterial thrombosis accounting for the majority (3.3%) (Vitiello, 1998). A study conducted by investigators from the United States Food and Drug Administration examining off-label medication use in children demonstrated that the results of 21% of pediatric dosing studies, revealed important new information leading to changed dosing recommendations (Roberts, Rodriguez, Murphy and Crescenzi, 2003). While numerous clinical trials in adults have resulted in the formation of comprehensive management guidelines, considerably less is known about the safety and efficacy of clopidogrel use in children. In addition, the available data has primarily been gathered from retrospective studies conducted at single centers, which decreases the strength of evidence thereby limiting its applicability in clinical practice.
Purpose of the Study

Eight in 1,000 infants are born with congenital heart defects. Fortunately, with advancing medical therapies and surgical interventions, more than ninety percent of these children survive to adulthood (Carr and King, 2010). Antiplatelet therapy is widely used in these children despite limited data specific to this population. The aim of this review is to examine the body of evidence on the use of clopidogrel in children, using the GRADE method to evaluate study outcomes, in an effort to strengthen conclusions regarding its safety and efficacy in the prevention of thrombotic events.

METHODS

An exhaustive literature search was performed using PubMed, Web of Science, Cochrane, Medline, CINAHL and International Pharmaceutical Abstracts. These databases were accessed through the Pacific University Library system. The keywords searched included "clopidogrel", "child", "teen", "young", "pediatric", "boy", "girl", "adolescent" and "heart diseases" individually and in combination. The search was limited to the English language and articles older than ten years were excluded resulting in the initial identification of 39 articles. After eliminating duplicate articles and those irrelevant to the topic of interest, seven studies were identified for review and three were selected (1 randomized-control trial and 2 retrospective chart reviews).

RESULTS

The first study reviewed was a prospective, multicenter, randomized, placebo-controlled trial (PICOLO), conducted by Li and colleagues, evaluating the pharmacodynamics, safety and tolerability of clopidogrel in children 0-24 months at risk for arterial thrombosis due to cardiac condition (Li et al, 2008). Most patients underwent interventions, including shunt, stent or graft placement, necessitating antiplatelet therapy. There were more males than females (37.2%) in the study and the majority of patients were Caucasian (84.9%). Twenty-
two centers across Belgium, Canada, France, Germany and the United States participated. Of the 339 eligible, 116 enrolled, 92 were randomized and 73 (34 neonates and 39 infants/toddlers) completed the study. Patients were stratified according to age (less than 30 days, and 30 days to 24 months) and randomized to clopidogrel versus placebo in a 3:1 ratio in four sequential groups (0.01, 0.10, 0.20 and 0.15 mg/kg/day) for seven to twenty-eight days. Of treated patients, 79% were taking concomitant acetylsalicylic acid (ASA). Study investigators were aware of the therapy cohort, but not whether the patient was to receive placebo or clopidogrel. Platelet aggregation was assessed at baseline and steady state, by light transmission aggregometry with 3.2% sodium citrate as an anticoagulant and 5 µmol/L ADP as the agonist. The primary outcome of interest was to achieve 30-50% inhibition of 5 µmol/L ADP-induced platelet aggregation in neonates, infants and toddlers with cardiac conditions, at risk for arterial thrombosis. It was determined that clopidogrel, 0.20mg/kg/day, in the study population was well tolerated and achieved comparable platelet inhibition as 75 mg/day in adults. The dose response was evaluated by the inhibition of the maximum extent of platelet aggregation and inhibition of rate of aggregation. Direct comparison of active dose groups produced significant results: 0.01 mg/kg versus 0.2 mg/kg (p = 0.0001 and p = 0.0328, respectively) and 0.1 mg/kg versus 0.2 mg/kg (p = 0.0078 and p = 0.0077, respectively). The daily dose of 0.2 mg/kg achieved the target mean of 30-50% inhibition of 5 µmol/L ADP-induced platelet aggregation. Ten patients discontinued the study drug for reasons including: adverse events (n = 3), bleeding (n = 2), death (n = 1), incorrect dosing (n = 1), guaic-positive stool (1) and other (n = 2). There were eight serious adverse events reported in six patients—three in those receiving placebo and five in those receiving clopidogrel, albeit only one occurrence, decreased platelet count, was determined to be possibly connected to the study drug. Minor bleeding occurred in four patients, two of whom were in the placebo group. One
patient became hemodynamically unstable, dying after receiving four, 0.15 mg/kg doses of clopidogrel, but the death was deemed unrelated to clopidogrel.

In the second study reviewed, Mertens et al performed a single center, retrospective chart review at the University Hospital in Leuven, Belgium, of children with heart disease in whom clopidogrel therapy was initiated during hospitalization for surgical procedures or interventional catheterization (Mertens, Eyskens, Boshoff and Gewillig, 2008). Forty-four of the forty-six children included had congenital heart disease. These children ranged in age from seven weeks to fifteen years old and varied in weight between 3.6-72.0 kg. Most patients (n =43) received concomitant ASA, two also received warfarin, two received a combination of clopidogrel and warfarin and one patient was on monotherapy with clopidogrel. Initially, doses of 0.5-1.0 mg/kg/day were used, which were based on the expected dose as deducted from adult studies. After the development of recurrent epistaxis in one patient, dosing was lowered to 0.2-0.3 mg/kg/day. The mean duration of treatment was 132.7 +/- 139.9 days (range 1-833 days) with daily doses between 0.1-0.7 mg/kg, adjusted on an individual basis and reduced in the presence of any adverse events. Those patients taking concomitant warfarin suffered major bleeding complications—severe epistaxis in one and gastrointestinal bleeding in the other; clopidogrel was consequently stopped in both. Ten patients suffered drug related adverse events, leading nine to withdraw from treatment (epistaxis (2), rash (2), skin bruising (2), hair loss (1), melena (1) and anemia with reduced white blood cell count), though the relationship to clopidogrel could not always be determined. Skin bruising was observed in most patients, but was only considered an adverse event if it was the reason for discontinuation, as it was regarded as a normal physiologic phenomenon reflecting the efficacy of clopidogrel. Although minor bleeding complications were relatively common, none warranted urgent medical care or hospitalization. Of note, this bleeding rate
(6%) was comparable or lower than in adult trials with clopidogrel. No thrombotic events or clots were detected in any of the treated patients.

Finkelstein and his team at The Hospital for Sick Children in Toronto conducted a retrospective chart review of all infants and children who received clopidogrel between January 2001 and April 2004, while hospitalized with congenital or acquired heart disease (Finkelstein, Nurmohamed, Avner, Benson and Koren, 2005). Of the fifteen children identified, four were less than twelve months old (six weeks to sixteen years) and the female to male ratio was 2:1. Fourteen patients underwent cardiac catheterization, ten of whom had stents placed. Clopidogrel was started in these patients as a component of primary thrombus prevention. It was also administered after thrombus formation in three patients. Among patients, dosing varied from 1 to 6 mg/kg/day. No loading doses were used. The duration of treatment varied between one and six months. Twelve of the children were taking ASA. In some cases anticoagulants were used in addition to clopidogrel. Heparin was administered to five children with diminished arterial pulses or when thrombus formation was demonstrated with ultrasound during the immediate post-catheterization period prior to beginning clopidogrel. Eleven patients had uncomplicated courses including unobstructed stents and experienced no adverse events. One patient with Ehlers-Danlos in whom a pulmonary artery stent was placed, developed extensive vascular thrombosis four and a half months after completing a six week course of clopidogrel. Another patient continued to experience a diminished femoral artery pulse three months after finishing a three month course of clopidogrel. Overall, only one adverse event was deemed due to clopidogrel. This patient suffered a massive upper gastrointestinal bleed leading to hypotension, after one month of a triple therapy regimen consisting of clopidogrel 1 mg/kg/day, warfarin 2.5 mg/day and ASA 80 mg/day. Therapy was discontinued immediately and the patient received vitamin K, blood products and inotropes. Five months after this incident, the child suffered a thrombotic
cerebral stroke and was consequently placed on clopidogrel 1 mg/kg for fourteen days. He received one additional fourteen day course of clopidogrel for an unclear indication, five months later and died from cardiac arrhythmia 2 weeks later.

DISCUSSION

While it has long been established that platelets play a vital role in both the normal physiologic processes of hemostasis, wound healing, inflammation and innate immunity, they also play a less favorable role in the pathologic process of thrombus formation (Li and Newburger, 2010). Although the incidence of thromboembolism, the development of a clot within the blood vessels, is considerably lower in children than adults, the morbidity associated with it is of clinical significance (Seth, 2009 and Odegard et al, 2007). There are important differences in the etiology of thrombus formation, platelet function and pharmacokinetics in children. Though the platelets of neonates and children are structurally similar to those of adults, they are hyporesponsive to activating stimuli, leading to decreased aggregation and secretion rates (Israels and Michelson, 2006). Children with heart disease frequently have abnormal blood flow patterns and/or polycythemia contributing to stasis and hyperviscosity. Many of these children must undergo cardiac procedures, which put them at greater risk through the iatrogenic complications associated with endothelial damage. Stasis, vascular damage and hypercoagulability are three independent factors in the development of thrombosis, commonly known as Vichow's triad. Furthermore antiplatelet therapy has been studied extensively in adults with cardiovascular and cerebrovascular diseases that put them at risk for clotting, but much less is known about these medications as used in the pediatric population.

Clopidogrel, a specific platelet aggregation inhibitor, commonly used for prevention of thromboembolic events, has been used off-label in children at risk for clot formation for more than a decade, despite limited studies evaluating its safety and efficacy in this population.
The PICOLO trial demonstrated that neonates and young children require a significantly lower dose of clopidogrel per kilogram of body weight than adults. Investigators examined four dosing regimens and determined clopidogrel 0.20 mg/kg/day, in those 0-24 months with systemic-to-pulmonary artery shunt or stent, achieves 30 to 50% platelet inhibition levels, comparable to those in adults taking the standard approved dose of 75 mg/day. Adverse events were not common, at this dose, and were rarely determined related to clopidogrel. Investigators recognized several factors which may limit the application of the study findings. Dosing groups were small and were not balanced with regards to age, ethnicity or diagnosis. There was no test for period effects, which are possible in studies with sequential randomization, though the authors felt the impact of this to be minimal since the study was conducted over a relatively short period. The study was not considered strictly intent to treat, since those participants who discontinued did not have follow-up platelet aggregation studies. With that said, there was no manner in which to determine if the aggregability in these patients would have been consistent with those who completed the study. Regarding platelet function, the study chose to assess ADP-induced aggregation solely because other tests would have required additional blood to be drawn from these young patients. The study did not test doses larger than 0.20 mg/kg/day nor did it define a dose at which the ceiling effect occurs in young children. Because the ceiling effect occurred at 50-60% inhibition in adult studies, the PICOLO trial made this the target. Overall, the authors felt clopidogrel to be well tolerated in infants and toddlers at the dose of 0.20 mg/kg/day. They emphasized the importance of proper application of the results, which should not be generalized to include all children with thrombotic disease.

The Mertens study reported on the use of clopidogrel in children with heart disease through the use of a retrospective chart review. During the early study period, doses of 0.5-1.0 mg/kg/day were used, however due to bleeding complications in the initial patients,
providers adjusted dosing to 0.2-0.3 mg/kg/day. Patients on concomitant anticoagulation therapy experienced more severe bleeding complications. The antiplatelet effect was assessed qualitatively as a function of skin bruising, which occurred in nearly every patient and by the absence of thrombotic events in all of those using clopidogrel during the study period. The additional use of ASA may have further reduced the risk of thrombosis through its perceived synergistic effect with clopidogrel on platelet inhibition. As with other studies examining this topic, the small study population limits the applicability of the results. The bleeding complication rate, for instance, which is as high as 5% in adults, and was similar or even lower in this trial, may have been underestimated due to the study size. Information was gathered retrospectively and, as such, investigators lose control over variables such as timing of medication administration, continuity of clinical laboratory monitoring, length of therapy and treatment follow-up. Since clopidogrel comes in two standard doses only, the tablets were crushed and compounded. At the time of the study, there was no pharmacodynamic data on crushed clopidogrel. Based on study findings, clopidogrel should be used cautiously in children and the adult dosing scheme is not appropriate because it does not account for key physiologic and metabolic differences between these populations (Mertens, Eyskens, Boshoff, and Gewillig, 2008).

Finkelstein and his colleagues found clopidogrel to be relatively well tolerated in children with heart disease, despite the high doses that were often used in this retrospective cohort study. There was one isolated severe complication—a gastrointestinal bleed in a child receiving triple antithrombotic therapy, but no other side effects or thrombotic events were reported. The small population size, relatively brief follow-up period, and varying dosages limit the influence of the study findings on the safety profile and efficacy of clopidogrel in the prevention of thromboembolic events. With the duration of therapy in children yet to be determined, researchers speculated that six months to be appropriate for primary prevention
since implanted devices appear to endothelialize within this period. Additionally researchers did not use an objective measurement of the inhibition of platelet aggregation. In summary, because there no guidelines were available regarding the recommendations for use in children, study investigators suggested initial doses of clopidogrel could be extrapolated from the adult regimen (Finkelstein, Nurmohamed, Avner, Benson, and Koren, 2005).

The study outcomes were analyzed according to the GRADE method (Appendix A). The quality of the results are somewhat limited due to the small populations in all three of the studies, which are reflected as a measure of imprecision. Two important outcomes assessed in the PICOLO trial were the percentage inhibitions of (1) maximal extent of platelet aggregation and (2) the rate of aggregation, which were determined to be dose dependent. In this study, researchers suggest that the variability in the percentage inhibition of platelet aggregation is consistent with the that seen in the adult population (Lau, 2004). Even with the notably wide confidence intervals in the PICOLO trial, the evidence for these outcomes was of high caliber as attributed, in part, by the clear dose dependent response to clopidogrel. All of the studies reviewed were interested in bleeding complications, classified as minor or major, that may be associated with clopidogrel. Though the quality of evidence for all bleeding events was low, both retrospective chart reviews demonstrated a slightly increased risk of major bleeding when on concomitant therapy with anticoagulants or additional antiplatelet medications. The retrospective studies also found that children taking clopidogrel had a decreased risk of experiencing a thrombotic event, which was anticipated to occur in as many as 12-33% of patients according to previous reports, though the evidence was of low quality (Balling, 2000). When considering all study important outcomes, the overall grade of evidence is low.
CONCLUSION

Implications for Practice

As best illustrated in the PICOLO trial, children seem to require considerably lower weight based doses of clopidogrel to achieve similar platelet inhibition levels to those adults taking the standard 75 mg/d dose (Li et al, 2008). While it is evident that dosing regimens extrapolated from the adult formula are not appropriate for infants and young children, studies involving older children are limited to retrospective reports, which provide lower quality evidence thereby limiting the application of their findings. In the studies reviewed, thrombotic events were very rare, though most infants and children were taking concomitant ASA and in some cases anticoagulants, making the efficacy of clopidogrel difficult to assess as it has not been directly compared to other therapies aimed at thrombus prophylaxis in this population. Based on current studies, clopidogrel seems reasonably well tolerated in children at low doses, but should be used cautiously, particularly when administered in combination with other antiplatelet or anticoagulants, as it may increase bleeding risks (Finkelstein et al, 2005 and Maltz, Gauvreau, Connor and Jenkins, 2009).

Implications for Research

With limited evidence from prospective trials, many loose ends remain regarding the use of clopidogrel in children with heart disease. Research in the adult population demonstrates the clear benefit of using a loading dose of 300 mg, which is reflected in current practice guidelines, however this has yet to be examined in children. Similarly, the appropriate duration of therapy, while likely differing based on diagnosis and intervention, has not been established. Because clopidogrel currently only comes in two doses, 75 mg and 300 mg, as appropriate for adult usage, when administered to children tablets must be compounded and is generally given as oral solution. One study showed faster absorption, greater peak plasma concentrations and increased bioavailability when using crushed, 300
mg tablets, administered via nasogastric tube versus use of conventional oral clopidogrel, however it is unclear whether these results are a function of crushing the tablets or the route of administration or a combination of both factors (Urooj Zafar, Farkouh, Fuster, and Chesebro, 2009). The ADP-induced hyporeactivity in young children, as suggested by Israels and Michelson, may contribute to the lower clopidogrel dose per kilogram requirement to achieve similar inhibition of platelet aggregation compared with adults (2006). With that said, additional mechanisms explaining the lower dose requirement have not been investigated. Some possible variables may include differences in clopidogrel absorption, metabolism through cytochrome P450 and the number of P2Y$_{12}$ receptors on each platelet (Li et al, 2008). Pediatricians and other providers who care for children are anxiously awaiting the results of the CLARINET trial, a multicenter, randomized, controlled trial, which aims to assess safety and efficacy of the previously established dose of clopidogrel 0.2 mg/kg/d in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt.
REFERENCES


