



ORIGINAL ARTICLE

What is the optimal dose of clopidogrel in paediatric patients? ☆



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Paediatrics;
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Abstract

Introduction: The aim of this study was to collect retrospective data on the prescription of clopidogrel, describe the conditions of its use in the paediatric population of a tertiary referral hospital, and evaluate its use based on the current scientific evidence.

Patients and methods: We conducted a retrospective, observational and descriptive study between March 2010 and March 2017. We included all patients under the age of 18 who were discharged from our hospital for home treatment with clopidogrel within the study period. We collected data on the following: demographic data, diagnosis, indication for clopidogrel, start and end date of treatment, presence or absence of concomitant treatment with acetylsalicylic acid or other antiplatelet or anticoagulant drugs, concomitant treatment with proton pump inhibitors, effectiveness, and adverse effects.

Results: The study included a total of 11 patients (45% male). The mean age was 3.1 years (range, 1 month to 8 years). The prescribed dose of clopidogrel was 0.2 mg/kg/day in all patients, and 10/11 patients received concomitant treatment with acetylsalicylic acid with the purpose of optimising antiplatelet therapy. None of the children received concomitant treatment with anticoagulants, and only one of them received treatment with a proton pump inhibitor. We did not find evidence of haemorrhagic complications or other adverse effects associated with clopidogrel.

Conclusion: Based on our experience, a clopidogrel dose of 0.2 mg/kg/day is a safe and effective treatment, regardless of the patient's age. The good tolerance observed in our study could be

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PALABRAS CLAVE

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related to the adjustment of the optimal dose with the aim of achieving antiplatelet aggregation without increasing the risk of adverse effects.

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¿Cuál es la dosis óptima de clopidogrel en pacientes pediátricos?**Resumen**

Introducción: El objetivo de este estudio fue recopilar datos retrospectivos sobre la prescripción de clopidogrel y describir las condiciones de uso en la población pediátrica de un hospital de referencia de nivel terciario y evaluarlas con base en la evidencia disponible.

Pacientes y métodos: Estudio observacional, descriptivo y retrospectivo realizado entre marzo de 2010 y marzo de 2017. Los criterios de inclusión fueron: 100% de los pacientes menores de 18 años que fueron dados de alta de nuestro hospital con clopidogrel como tratamiento domiciliario en el período de estudio. Se recogieron los siguientes datos: datos demográficos, diagnóstico, indicación de clopidogrel, fecha de inicio y de finalización del tratamiento, presencia o ausencia de tratamiento concomitante con ácido acetilsalicílico u otros antiagregantes plaquetarios o anticoagulantes, tratamiento concomitante con inhibidores de la bomba de protones, efectividad y efectos adversos.

Resultados: Un total de 11 pacientes se incluyeron en el estudio (45% hombres). La edad promedio fue de 3,1 años (rango: 1 mes-8 años). La dosis recomendada de clopidogrel fue de 0,2 mg/kg/día en todos los individuos, recibiendo tratamiento concomitante con ácido acetilsalicílico 10/11 pacientes para optimizar la terapia antiplaquetaria. Ningún niño recibió tratamiento concomitante con anticoagulantes y solo uno de ellos recibió tratamiento con inhibidores de la bomba de protones. No se observaron trastornos hemorrágicos u otros efectos adversos asociados con clopidogrel.

Conclusión: Según nuestra experiencia, la dosis de clopidogrel de 0,2 mg/kg/día demostró ser una estrategia segura y efectiva, independientemente de la edad del paciente. La buena tolerancia observada podría estar asociada con el ajuste de la dosis óptima para lograr la antiagregación plaquetaria sin aumentar el riesgo de efectos adversos.

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Introduction

Clopidogrel is a prodrug derived from thienopyridine. It is metabolised by CYP450 to its active metabolite, which irreversibly and selectively blocks the adenosine-diphosphate (ADP) bond to its P2Y₁₂ platelet receptor and the subsequent activation of the ADP-mediated GPIIb-IIIa complex, thereby inhibiting platelet aggregation.¹

As it is administered orally and does not require monitoring of its blood levels or its antiplatelet activity according to its summary of product characteristics, clopidogrel offers an attractive alternative for treatment of paediatric patients at risk of thrombotic events.²

The PICOLO clinical trial (2008) showed that in children aged 0–24 months, a dose of clopidogrel of 0.2 mg/kg/day achieved a suitable inhibition of platelet function, comparable to the effect observed in adults with a dose of 75 mg/day.³

Little information has been published to date on the use of clopidogrel in children over the age of 2 years, and the available literature is limited to case series where there

were significant differences in the administered doses of clopidogrel (0.2–9 mg/kg/day).^{2,5–8}

The aim of this article was to describe our experience with the use of clopidogrel in paediatric patients and the conditions of its use in a tertiary level hospital that is a referral centre for heart surgery and paediatric heart disease, and to evaluate this use based on the current evidence.

Materials and methods

We conducted a retrospective, observational and descriptive study on the use of clopidogrel in paediatric patients. The study included every patient under the age of 18 years who were discharged from our hospital for home treatment with clopidogrel between March 2010 and March 2017.

We identified patients by searching the electronic prescription database and the register of off-label medication dispensed by our pharmacy department. We reviewed the electronic clinical records using the IANUS® (the institutional electronic health record database of the Galician Health Service) and the ICIP® (Philips) applications, collecting data

on the following: demographic variables, diagnosis, indication for clopidogrel, start and end date of treatment, use or lack thereof of concomitant treatment with acetylsalicylic acid or other antiplatelet or anticoagulant drugs, use or lack thereof of concomitant treatment with proton pump inhibitors (PPIs), effectiveness, and adverse effects associated with treatment. We considered effectiveness adequate if there were no documented no arterial thrombotic or thromboembolic events. We did not find evidence of any haemorrhagic complications or other adverse effects associated with the use of clopidogrel.

We consulted the Uptodate[®] and Micromedex[®] databases to compare our experience with the current scientific evidence (April 2017).

Results

We included a total of 11 patients in the study (Table 1), 5 male and 6 female, with a mean age of 3.1 years (range, 1 month to 8 years). All patients received an oral solution of clopidogrel 5 mg/mL prepared by the hospital pharmacy. Every patient had some type of hemodynamically significant congenital heart disease. The indication for administering clopidogrel was the prevention of arterial thrombotic and thromboembolic events associated with cardiac surgery or catheter-based interventions. Treatment with clopidogrel was initiated after implantation of one or more stents in all patients, with the exception of one patient in whom it was indicated following distal aortic arch reconstruction with anastomosis and sectioning of the ductus.

The prescribed dose was 0.2 mg/kg/day in all patients, with 10/11 patients receiving concomitant treatment with acetylsalicylic acid (mean dose, 4.8 mg/kg/day; range, 3.6–5.8 mg/kg/day) to optimise the antiplatelet therapy. None of the patients received concomitant treatment with anticoagulant agents, and only one patient received treatment with PPIs. The mean duration of antiplatelet therapy was 58 days; median duration: 39 days (range, 24–139 days). No arterial thrombotic or thromboembolic events were documented. There was no record of haemorrhagic complications or other adverse effects associated with the use of clopidogrel. The platelet count remained within normal range in all cases, and none of the patients died during the followup (30 days to 5 years, depending on the patient).

The literature describes two groups of patients that would receive different doses of clopidogrel based on their age: a first group that would include all patients under age 2 years (dose of 0.2 mg/kg/24 h), and a second group including all patients aged more than 2 years (dose of 1 mg/kg/24 h). In our hospital, the prescribed dose of clopidogrel was 0.2 mg/kg/24 h regardless of the age of the patient (6 patients in our study were more than 2 years old).

Discussion

For a clinical practice to be considered adequate, it has to be validated based on objective data on its efficacy and safety. This validation process is based on clinical trials. The need to carry out specific research in the paediatric population stems from the differences in physiological and

psychological development relative to adults, which could result in specific responses to treatment and different safety profiles. However, clinical research in paediatrics is hindered by the fact that children are considered a vulnerable group that requires special protection as well as the limited economic appeal of many paediatric clinical trials for the pharmaceutical industry, and off-label prescriptions amount to 30% to 90% of the total in this age group.⁹

The main problems caused by the lack of drugs specifically approved for children are the absence of suitable formulations for their correct administration and a lack of data regarding their optimal dose, specific toxicity and long-term safety. In the case of clopidogrel, the current literature recommends two dose ranges depending on whether the child is aged more or less than 24 months.

The dose for newborns and children up to age 2 years recommended in literature (0.2 mg/kg/day) derives from two clinical trials (PICOLO and CLARINET) that included a total of 998 patients. The results of the PICOLO trial showed that a dose of 0.2 mg/kg/day of clopidogrel in children aged 0–24 months achieved adequate inhibition of platelet function, comparable to that achieved in adults with a dose of 75 mg/day (approximately 1 mg/kg/day). In this study, 79% of the included children received acetylsalicylic acid as a concomitant treatment, and none experienced serious haemorrhagic events.³ The CLARINET trial included children under 93 days of age with cyanotic congenital heart disease and systemic-to-pulmonary artery shunts who were treated with 0.2 mg/kg/day of clopidogrel added to conventional therapy, which included acetylsalicylic acid in 87.9% of the patients. The addition of clopidogrel to conventional treatment did not lead to an increase in efficacy and was associated with a 0.7% increase in the incidence of severe haemorrhage.⁴

The dose of clopidogrel suggested for children aged more than 2 years in the literature has been derived from several case reports, with significant differences in the administered doses, which have ranged from 0.2 to 9 mg/kg/day.

Finkelstein et al. carried out a retrospective review of 15 patients (mean age, 3.5 years; range, 6 weeks to 16 years) with congenital and acquired heart disease treated with clopidogrel at doses ranging from 1 to 6 mg/kg/day. They reported no thrombotic events, although one patient experienced gastrointestinal bleeding under triple antithrombotic therapy (clopidogrel, warfarin and acetylsalicylic acid).⁵

Soman et al. carried out a prospective study of 17 patients (mean age, 8.8 years; range, 1.5–17 years) that had suffered ischaemic strokes and were treated with clopidogrel because they did not tolerate or respond to treatment with acetylsalicylic acid. The prescribed doses of clopidogrel ranged between 0.5 and 2.4 mg/kg/day. Two patients experienced subdural haematomas while receiving treatment with clopidogrel combined with acetylsalicylic acid.⁸

In a retrospective study that included 90 patients (mean age, 6.7 years; range, 11 days to 17.9 years) treated with clopidogrel (mainly for cardiac disease), Maltz et al. reported a mean dose of 1.3 mg/kg/day (range, 0.2–8.9 mg/kg/day) and haemorrhagic complications in 4.4%.²

When it comes to its pharmacokinetics, clopidogrel is quickly absorbed after oral ingestion, reaching its peak plasma concentration 45 minutes after administration. It

Table 1 Patients, sex (M= male, F= female), age, diagnosis, treatment (clopidogrel, ASA = acetylsalicylic acid, ACO = anticoagulant therapy, PPI = proton pump inhibitor).

Patient	Sex	Age	Diagnosis	Treatment			
				Clopidogrel	ASA	ACO	PPIs
1	M	5 months	Tetralogy of Fallot	0.20 mg/kg/24 h (68 days)	YES	NO	NO
2	M	1 month	Shone syndrome	0.18 mg/kg/24 h (139 days)	NO	NO	NO
3	F	8 months	Tetralogy of Fallot	0.2 mg/kg/24 h (30 days)	YES	NO	NO
4	F	4 years	Pulmonary stenosis	0.22 mg/kg/24 h (135 days)	YES	NO	YES
5	M	7 years	Pulmonary atresia	0.20 mg/kg/24 h (30 days)	YES	NO	NO
6	F	2 months	Tetralogy of Fallot	0.24 mg/kg/24 h (25 days)	YES	NO	NO
7	M	1 month	Congenital pulmonary valve disease	0.20 mg/kg/24 h (24 days)	YES	NO	NO
8	F	8 years	Tetralogy of Fallot	0.18 mg/kg/24 h (60 days)	YES	NO	NO
9	F	6 years	Complex congenital heart disease	0.21 mg/kg/24 h (60 days)	YES	NO	NO
10	F	5 years	Hypoplastic left heart syndrome	0.21 mg/kg/24 h (39 days)	YES	NO	NO
11	M	3 years	Pulmonary atresia	0.23 mg/kg/24 h (30 days)	YES	NO	NO

is estimated that less than 50% of the dose is absorbed (calculated based on the urinary excretion of its metabolites), and is then eliminated by the kidneys (50%) or in faeces (46%).¹ Clopidogrel is a prodrug that has to be metabolised via CYP450 to produce the active metabolite that inhibits platelet aggregation. It is mainly metabolised via two metabolic routes: one that is esterase-mediated, leading to hydrolysis in its carboxylic derivative, and another that is mediated by multiple cytochrome P450 enzymes. The active metabolite, a thiol derived from clopidogrel, is mainly formed by the action of CYP2C19 with the contribution of various CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. As the action of cytochrome CYP2C19 is required for clopidogrel to be transformed into its active metabolite, we may expect that the greater the patient's enzymatic CYP activity, the more clopidogrel will be activated. Taking into account that the glomerular filtration rate is estimated to be 100–120 mL/min/1.73 m² from age 1 year, similar to the rate in adults,¹⁰ and that the expression and activity of the cytochrome CYP enzymes increase with age (from birth until reaching adulthood),¹¹ we did not find any justification from a pharmacokinetic or pharmacogenetic perspective for the differences in the dosage of clopidogrel based on age recommended in some publications: 0.2 mg/kg/day for children under the age of 2, and 1 mg/kg/day for children over the age of 2.

This does not mean that the pharmacogenetics of cytochrome CYP are not important in the dosing of clopidogrel. There are several studies that demonstrate the relationship between CYP polymorphisms and the antiplatelet activity of thienopyridines.^{12–14} As early as 2010, the European Medicines Agency (EMA) already warned that the efficacy of clopidogrel could be reduced with the concomitant use of omeprazole or esomeprazole or other CYP2C19 inhibitors (EMA/174948/2010). There is no doubt that pharmacogenetics and pharmacodynamics are important in the activity of clopidogrel.

We think that a possible explanation for the different doses found in the literature in children older than two years old may be due to the fact that the published studies

are case series that include few patients where the existing pharmacogenetic differences in CYP cytochromes could have a significant effect and lead to different outcomes. Clinical trials in paediatric patients aged more than 24 months are needed in order to establish the optimal dosage of clopidogrel and its safety profile in this age group, allowing the development of an evidence-based treatment protocol.

In our study, a dose of clopidogrel of 0.2 mg/kg/day was prescribed to all patients regardless of whether they aged more or less than 2 years, and 10 out of the 11 patients received concomitant treatment with acetylsalicylic acid. We consider the dose of 0.2 mg/kg/day of clopidogrel effective, as no arterial thrombotic or thromboembolic events were documented. We also consider it a safe dose, since none of the patients experienced haemorrhagic complications, and the patients' platelet counts remained within normal ranges throughout the followup. Our study has the limitations intrinsic to a retrospective, observational and descriptive study based on a review of health records in a small population.

Conclusion

In our hospital, clopidogrel is usually prescribed to prevent arterial thrombotic and thromboembolic events associated with heart surgery or catheter-based interventions in patients with complex heart defects. In our experience, clopidogrel administered at a dose of 0.2 mg/kg/day, in most cases in combination with acetylsalicylic acid (mean dose, 4.8 mg/kg/day, range, 3.6–5.8 mg/kg/day) proved to be a safe and effective strategy, regardless of patient age. However, we did not take into account genetic polymorphisms, which may help determine whether a patient may require higher or lower doses. The good tolerance observed in our study could be associated with having adjusted the optimal dose in order to achieve ADP-induced platelet aggregation without increasing the risk of adverse effects. We consider that the optimal dosage of clopidogrel should be determined

based on the pharmacokinetic profile of the patient, and not on the patient's age.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Technical data sheet for Plavix 75 mg coated tablets. Available from: https://cima.aemps.es/cima/dochtml/ft/98069001/FT_98069001.HTML
2. Maltz LA, Gauvreau K, Connor JA, Jenkins KJ. Clopidogrel in a pediatric population: prescribing practice and outcomes from a single center. *Pediatr Cardiol*. 2009;30:99–105, <http://dx.doi.org/10.1007/s00246-008-9289-x>.
3. Li JS, Yow E, Berezny KY, Takahashi M, Graham TP Jr, Sanders SP, et al. Dosing of clopidogrel for platelet inhibition in infants and young children: primary results of the Platelet Inhibition in Children On cLOpidogrel (PICOLO) trial. *Circulation*. 2008;117:553–9, <http://dx.doi.org/10.1161/CIRCULATIONAHA.107.715821>.
4. Finkelstein Y, Nurmohamed L, Avner M, Benson LN, Koren G. Clopidogrel use in children. *J Pediatr*. 2005;147:657–61, <http://dx.doi.org/10.1016/j.jpeds.2005.05.006>.
5. Hanke CA, Stiller B, Nakamura L, Grohmann J, Zieger B. Prophylactic use of clopidogrel in paediatric cardiac patients. *Klin Padiatr*. 2012;224:166–9, <http://dx.doi.org/10.1055/s-0032-1306345>.
6. Mertens L, Eykens B, Boshoff D, Gewillig M. Safety and efficacy of clopidogrel in children with heart disease. *J Pediatr*. 2008;153:61–4, <http://dx.doi.org/10.1016/j.jpeds.2007.12.050>.
7. Soman T, Rafay MF, Hune S, Allen A, MacGregor D, deVeber G. The risks and safety of clopidogrel in pediatric arterial ischemic stroke. *Stroke*. 2006;37:1120–2.
8. Fernández Uzquiano E, Lavilla Uriol P, Gil Aguado A. Ensayos clínicos en pediatría. *An Pediatr Contin*. 2008;6:361–3.
9. Wessel DL, Berger F, Li JS, Dähnert I, Rakhit A, Fontecave S, et al., CLARINET investigators. Clopidogrel in infants with systemic-to-pulmonary-artery shunts. *N Engl J Med*. 2013;368:2377–84, <http://dx.doi.org/10.1056/NEJMoa1114588>.
10. Fernández C, Espinosa L. Pruebas de función renal. *An Pediatr Contin*. 2008;6:93–7.
11. Molina Ortiz D, Camacho Carranza R, Domínguez Ramírez AM, Vences Mejía A. Modulación de la expresión de enzimas del citocromo P450 hepáticas durante las etapas fetal y pediátrica. *Rev Educ Bioquímica*. 2012;31:60–71.
12. Styles L, Heiselman D, Heath LE, Moser BA, Small DS, Jakubowski JA, et al. Prasugrel in children with sickle cell disease: pharmacokinetic and pharmacodynamic data from an open-label, adaptive-design, dose-ranging study. *J Pediatr Hematol Oncol*. 2015;37:1–9, <http://dx.doi.org/10.1097/MPH.0000000000000291>.
13. Price MJ, Murray SS, Angiolillo DJ, Lillie E, Smith EN, Tisch RL, et al. Influence of genetic polymorphisms on the effect of high- and standard-dose clopidogrel after percutaneous coronary intervention: the GIFT (Genotype Information and Functional Testing) study. *J Am Coll Cardiol*. 2012;59:1928–37, <http://dx.doi.org/10.1016/j.jacc.2011.11.068>.
14. Visscher H, Amstutz U, Sistonen J, Ross CJ, Hayden MR, Carleton BC. Pharmacogenomics of cardiovascular drugs and adverse effects in pediatrics. *J Cardiovasc Pharmacol*. 2011;58:228–39, <http://dx.doi.org/10.1097/FJC.0b013e3182163b82>.