Artículo Original de Investigación

Clopidogrel resistance in extremely high cardiovascular risk patients with genotype CYP2C19

Resistencia al clopidogrel en pacientes con extremado alto riesgo cardiovascular con genotipo CYP2C19

Liliana Cárdenas, MD[1]; Ali Aymen Abdullah MD[1]; Gabriela Jaramillo, PhD[1]; Paúl Cárdenas, MD, PhD[2]; Gabriela Gálvez, BSc[1]; Fernando Hidalgo, MD[1].

Coronary Care Unit of the Hospital de Especialidades Eugenio Espejo, Quito, Ecuador.

1 Cardiology Service, Hospital Eugenio Espejo, Quito, Ecuador. 2 Instituto de Microbiología, Universidad San Francisco de Quito, Quito, Ecuador.

INFORMACIÓN DEL ARTÍCULO

Recibido el 19 de Marzo de 2023
Aceptado después de revisión
el 22 de Agosto de 2023
www.revistafac.org.ar

There are no conflicts of interest to disclose.

Keywords:
Cytochrome P-450 CYP2C19;
cardiovascular disease;
clopidogrel;
drug resistance;
platelet antiaggregants

ABSTRACT

Identifying risk factors is of utmost importance in patients with cardiovascular risk, even more so in those with extremely high risk, who still present with complications despite receiving treatment as secondary prevention. We hypothesized that patients with very high cardiovascular risk would have genetic resistance to the antiplatelet agent clopidogrel. We performed a cross-sectional descriptive study that included 58 patients with the CYP2C19 genotype in the coronary care unit of the hospital, who were divided into two groups: resistant and non-resistant to therapy. We confirmed that patients in extremely high cardiovascular risk had more genetic resistance to clopidogrel, which caused secondary prevention failure, so they would benefit from individualizing antiplatelet therapy. .

Palabras clave:
Citocromo P-450 CYP2C19;
enfermedad cardiovascular;
clopidogrel;
resistencia a medicamento;
antiagregante plaquetario.

Resistencia al clopidogrel en pacientes con extremado alto riesgo cardiovascular con genotipo CYP2C19

RESUMEN

Identificar los factores de riesgo es de suma importancia en pacientes con riesgo cardiovascular, más aún en aquellos con riesgo extremadamente alto, que aún presentan complicaciones a pesar de recibir tratamiento como prevención secundaria. Presumimos que los pacientes con riesgo cardiovascular muy alto tendrían resistencia genética al antiagregante clopidogrel. Se realizó un estudio descriptivo transversal que incluyó a 58 pacientes con el genotipo CYP2C19 en la unidad de cuidados coronarios del hospital, los cuales fueron divididos en dos grupos: resistentes y no resistentes a la terapia. Se comprobó que los pacientes de extremado alto riesgo cardiovascular tenían más resistencia genética a clopidogrel, lo que provocaba el fracaso de la prevención secundaria, por lo que se beneficiarían de individualizar el tratamiento antiagregante.

INTRODUCCIÓN

In extremely high cardiovascular-risk patients, there is an increased incidence of failure of secondary prevention, making it very important to identify residual risk factors to change the course of the disease. A targeted therapy would reduce ischemic risk without increasing the one of bleeding. Clopidogrel is the most widely used antiplatelet drug, which is low-cost and easy to get. Additionally, there is no restriction from the Ministry of Health for its sale.

Platelet aggregation starts the arterial thrombotic process. Hyperreactivity is an exaggerated response to agonists, and treatment failure relates to more ischemic events. Between 4 and 30% of patients present an inadequate response due to genetic, cellular, and clinical factors. The greater the platelet volume, the more thrombotic potential, failure in revascularization, and resistance to anti-aggregates. Several consensuses alert about the poor efficacy of clopidogrel; even so, there is no standardization in definitions, methods, and techniques. There are two ways to evaluate its resistance: platelet function and study of the CYP2C19 genotype; the latter one is higher according to the North American consensus of 2019 since there is no variability of

Corresponding author's address:: **Dr. Aymen Ali**. DPostal address: Ecuador, Quito, 170502. *e-mail*: aymen1231@hotmail.com

the results, they do not change over time, and there are no external influences; the disadvantage is not recognizing resistance due to acquired causes. Only 15% of the dose is activated by cytochrome P450, so irreversibly inhibits the ADP receptor P2Y12, which is dose and time-dependent. Each cytochrome P450 gene is called by the acronym CYP, encoded by the CYP2C19 gene; it is highly polymorphic and is involved in the metabolism of several medications explaining the interindividual variability of their response; enzyme activity may be none or intermediate depending on the number of affected alleles (CYP2C19*2/CYP2C19*3), associated with more ischemic events, the *17 allele is an ultra-rapid metabolizer related to bleeding. Impaired enzyme activity has an autosomal recessive inheritance pattern. Regulatory agencies such as the FDA (Food and Drug Administration) and the EMA (European Medicine Agency) recognize CYP2C19 as an important pharmacogenetic biomarker for 22 drugs, and the CPIC (Clinical Pharmacogenetics Implementation Consortium) recommends against their use in intermediate or poor metabolizers. There are ethnic differences in their expression, the CYP2C19*3 polymorphism is less common in Hispanics. The more alleles affected, the less active metabolite: one variant or an intermediate metabolizer activates 26 to 31%, and two variants lead to no activation. The mutation of the intestinal transporter gene (ABCB1) decreases the bioavailability of clopidogrel and is associated with a worse prognosis if CYP2C19 polymorphisms coexist. We hypothesized that patients with extremely high cardiovascular risk would have genetic resistance to clopidogrel. The objective was to identify the relation of the CYP2C19 genotype in extremely high cardiovascular risk patients who take clopidogrel. To determine clinical, laboratory, and demographic characteristics that could represent residual risk. To establish the incidence of new atherosclerotic events or bleeding when adding another antiaggregant.

MATERIALS AND METHODS

This is a cross-sectional descriptive study, that included patients of the coronary care unit of the Eugenio Espejo Hospital between 2017 and 2018, studied for a CYP2C19 genetic polymorphism and coronary events (acute or chronic), exceptionally high-risk individuals taking secondary prevention with clopidogrel. Clinical, laboratory, demographic, and genetic data were obtained from the medical records (Hospital and Infinity systems). Extremely high cardiovascular-risk patients were defined as those diagnosed of acute coronary syndrome (ACS) and a left ventricular ejection fraction (LVEF) below 35%.

Patients with type 2 infarction were excluded. The data were compared between the resistant and non-resistant individuals as measured by CYP2C19 polymorphism. New atherosclerotic events, death, and bleeding were registered.

All participants signed informed consent for participating in this study.

RESULTS

In total, we identified 58 patients with the CYP2C19 genotype included in the study, 84% had extremely high risk as defined by low LVEF and ACS. The remaining 16% did not meet these criteria. In the extremely high risk group, two subgroups were identified: resistant and non-resistant, most were male gender in both sets, and the mean age was similar (56.5 years). The resistance distribution was intermediate enzymatic activity at 67% and no enzymatic activity at 33%. Obesity, diabetes, and smoking were more prevalent in the non-resistant group; hypertension, dyslipidemia, and renal failure were more frequent in the other group. Regarding previous cardiovascular events, patients with resistance suffered more myocardial infarctions (76.5% vs. 65%) and heart failure (11.8% vs. 10%) with $p<0.001$ and were revascularized with greater frequency. Most resistant patients used clopidogrel (61% vs. 57%). There was no relation to the use of omeprazole or morphine. Platelet volume was not an aggravating factor. The resistant individuals had more infarcts without ST elevation (33.3% vs. 22.5%), unstable angina (33.3% vs. 27.5%), and stable ischemia (16.7% vs. 10%) in contrast to myocardial infarction with ST elevation was more frequent in the non-resistant group (41.7% vs. 42.5%) $p>0.001$. There was also a statistical difference in clinical treatment (29.4% vs. 25%) and surgical revascularization (5.9% vs. 5%) in resistant patients, responders to clopidogrel had more stent treatment (64.7% vs. 67.5%). In resistant patients most commonly, two coronary arteries were affected (41.2% vs. 32.5%) and the anterior descending artery, with a statistical difference (72.5% vs. 66.7%). In the follow-up, most events occurred in resistant patients (29.4% vs. 17.5%) with incomplete revascularization (29% vs. 10%), which would reflect more complex coronary artery anatomy, with no statistical difference. Ticagrelor was the alternative antiaggregant in the two groups (few required anticoagulation because of atrial fibrillation or ventricular thrombus). The geographical distribution of the resistant individuals was mainly the provinces of Pichincha and Tungurahua, the majority were mixed race (one Caucasian). The CRUSADE scale did not show a high risk of bleeding.

DISCUSSION

The importance of this work is the inclusion of patients at extremely high risk, in whom secondary prevention failed to reduce ischemic events, a risk that lasts for years. The guidelines recommend double antiplatelet therapy for at least one year after an acute myocardial infarction, regardless of the chosen treatment. It was verified that there was more use of clopidogrel in the genetic resistance group. The factors related to increased platelet reactivity: smoking (paradoxical action), diabetes, and obesity, that influence platelet receptors with abnormal signals were more frequent in the non-resistant group, platelet function was not measured to identify an acquired resistance. We found a statistically significant difference in the cardiovascular history,

the infarction was more frequent in the resistant group, a condition that already qualifies them as high risk, they also had more previous percutaneous revascularization procedures, but we cannot prove that there was stent thrombosis. The new event was coronary syndrome without ST elevation and stable cardiopathy in the resistant group, while ST-elevation infarction occurred in non-resistant patients, with a statistically significant difference.

Most of the works that studied resistance to clopidogrel were in patients with myocardial infarction, a higher-risk phenotype, we included all the coronary phenotypes. Observational and prospective studies have shown that non-responders and low responders have more cardiovascular events, and targeted therapy offers better results and less bleeding. The last North American Consensus states that identifying the CYP2C19 genotype is helpful as a prognostic factor in patients at high ischemic risk, such as the ones in our study, especially if the treatment is percutaneous. Scaling antiplatelet therapy is only accepted for high-risk stable coronary disease. Therapy is not recommended for acute coronary syndromes because there is no evidence. The treatment of a new event that was performed the most was angioplasty, followed by clinical treatment, and very few required surgical revascularization. The platelet volume, a determining factor in platelet hyperreactivity, was irrelevant to our patients.

CONCLUSIONS

Patients at extreme risk had more genetic resistance to clopidogrel, so it should be considered as a cause of failure of secondary prevention, these individuals had more coronary events, namely non-ST-elevation coronary syndrome and stable cardiopathy, in whom we should study genetic resistance to individualize antiplatelet treatment. Studying CYP2C19-mediated resistance should be considered in all types of treatment, not only percutaneous. Diabetes, obesity, and smoking, known factors for increased platelet reactivity, were more prevalent in the non-resistant group. Patients with the resistance measured with CYP2C19 had a new atherosclerotic event during follow-up, although there was no statistically significant difference.

Acknowledgements

The author and all co-authors participated in the conduction of the present study and elaboration of this paper.

REFERENCES

1. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the management of patients with Non-ST-Elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 64: e139 – e228.
2. Gallone G, Baldetti L, Pagnesi M, et al. Medical Therapy for Long-Term Prevention of Atherothrombosis Following an Acute Coronary Syndrome: JACC State-of-the-Art Review. J Am Coll Cardiol **2018**; 72: 2886 – 2903.
3. Sibbing D, Aradi D, Alexopoulos D, et al. Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding P2Y(12) Receptor Inhibitor Treatment in Percutaneous Coronary Intervention. JACC Cardiovasc Interv **2019**; 12: 1521 – 1537.
4. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in Individual Responsiveness to Clopidogrel. Clinical Implications, Management, and Future Perspectives. J Am Coll Cardiol **2007**; 49: 1505 – 1516.
5. Koupenova M, Kehrel BE, Corkrey HA, et al. Thrombosis and platelets: An update. Eur Heart J **2017**; 38: 785 – 791.
6. Bonello L, Tantry US, Marcucci R, et al. Impact of Platelet Reactivity on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease. J Am Coll Cardiol **2018**; 13: 1505 – 1516.
7. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: A review of the evidence. J Am Coll Cardiol **2005**; 45: 1157 – 1164.
8. Uzel H, Özpelit E, Badak Ö, et al. Diagnostic accuracy of mean platelet volume in prediction of clopidogrel resistance in patients with acute coronary syndrome. Anadolu Kardiyol Derg **2014**; 14: 134 – 139.
9. Kırbaş Ö, Kurmuş Ö, Köseoğlu C, et al. Association between Admissions Mean Platelet Volume and ST Segment Resolution after Thrombolytic Therapy for Acute Myocardial Infarction. J Am Coll Cardiol **2014**; 62: C21.
10. Jiang P, Yuan J, Song Y, et al. TCT-817 Prognostic significance of mean platelet volume in diabetic patients with stable coronary 7 artery disease. J Am Coll Cardiol **2017**; 70: B332.
11. Xu J, Zhao X, Lu C. GW26-e4568 Mean Platelet Volume is the Predictor of Poor Myocardial Perfusion post Primary PCI. J Am Coll Cardiol **2015**; 66: C149 – C150.
12. Sibbing D, Aradi D, Alexopoulos D, et al. Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding P2Y12 Receptor Inhibitor Treatment in Percutaneous Coronary Intervention. JACC Cardiovasc Interv **2019**; 12: 1521 – 1537.
13. Savcic M, Hauert J, Bachmann F, et al. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. Semin Thromb Hemost **1999**; 25 (Suppl 2): 1 5–19.
14. ACC News Story. TAILOR-PCI: Genotype-guided Antiplatelet Therapy Post PCI Misses Mark. Available at https://www.acc.org/Latest-in-Cardiology/Articles/2020/03/24/16/41/sat-9am-TAILOR-PCI-Clinical-Implementation-Clopidogrel-Pharmacogenetics-acc-**2020** Accessed August 22nd, 2023.
15. Botton MR, Whirl-Carrillo M, Del Tredici AL, e al. PharmVar GeneFocus: CYP2C19. Clin Pharmacol Ther **2021**; 109: 352 - 366.
16. De Andrés F, Sosa-Macías M, Llerena A. A rapid and simple LC-MS/MS method for the simultaneous evaluation of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 hydroxylation capacity. Bioanalysis **2014**; 6: 683 – 696.
17. Johnson JA, Gong L, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. Clin Pharmacol Ther **2016**; 90: 1 – 28.
18. Holmes DR, Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: Approaches to the FDA "boxed warning": A report of the American college of cardiology foundation task force on clinical expert consensus documents and the American heart association. J Am Coll Cardiol **2010**; 56: 321 – 341.

19. Ambrosetti M, Abreu A, Corrá U, et al et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol **2021**; 28: 460 – 495.
20. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task force for the 8 management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of . Eur Heart J **2016**; 37: 267 – 315.
21. Sibbing D, Gross L. Smoking and Clopidogrel Response Revisited: Hemoglobin Levels Explaining the Smoker's Paradox*. JACC Cardiovasc Interv **2016**; 9: 1691 – 1693.
22. Price MJ. Diabetes mellitus and clopidogrel response variability. J Am Coll Cardiol **2014**; 64: 1015 – 1018.
23. Bhatt DL. What Makes Platelets Angry. Diabetes, Fibrinogen, Obesity, and Impaired Response to Antiplatelet Therapy? J Am Coll Cardiol **2008**; 52: 1060 – 1061.
24. Deiman BALM, Tonino PAL, Kouhestani K, et al. Reduced number of cardiovascular events and increased cost effectiveness by genotype-guided antiplatelet therapy in patients undergoing percutaneous coronary interventions in the Netherlands. Netherlands Hear J **2016**; 24: 589 – 599.
25. Sánchez-Ramos J, Dávila-Fajardo CL, Toledo Frías P, et al. Results of genotype-guided antiplatelet therapy in patients who undergone percutaneous coronary intervention with stent. Int J Cardiol **2016**; 225: 289 – 295.
26. Cavallari LH, Lee CR, Beitelshees AL, et al et al. Multisite Investigation of Outcomes with Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. JACC Cardiovasc Interv **2018**; 11: 181 – 191.
27. Roberts JD, Wells GA, Le May MR, et al. Point-of-care genetic testing for personalization of antiplatelet treatment (RAPID GENE): A prospective, randomised, proof-of-concept trial. Lancet **2012**; 379: 1705 – 1711.
28. Xie X, Ma YT, Yang YN, et al. Personalized antiplatelet therapy according to CYP2C19 genotype after percutaneous coronary intervention: A randomized control trial. Int J Cardiol **2013**; 168: 3736 – 3740.
29. Shen DL, Wang B, Bai J, et al. Clinical Value of CYP2C19 genetic testing for guiding the antiplatelet therapy in a Chinese population. J Cardiovasc Pharmacol **2016**; 67: 232 – 236.
30. Notarangelo FM, Maglietta G, Bevilacqua P, et al. Pharmacogenomic Approach to Selecting Antiplatelet Therapy in Patients With Acute Coronary Syndromes: The PHARMCLO Trial. J Am Coll Cardiol **2018;** 71: 1869 – 1877.