Original and generic clopidogrel: A comparison of antiplatelet effects and active metabolite concentrations in patients without polymorphisms in the *ABCB1* gene and the allele variants *CYPC19*2* and **3*

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Abstract

Background. Ticagrelor and prasugrel are widely used as antiplatelet therapy after coronary angioplasty. However, there is a group of patients with indications for clopidogrel treatment. This population includes patients with chronic or acute coronary syndrome who are treated invasively and have contraindications to the use of novel antiplatelet drugs due to antithrombotic treatment (particularly with non-vitamin K antagonist oral anticoagulants). A wide range of generic forms of clopidogrel are available on the market. However, it is unclear whether they are as effective as the originator drug.

Objectives. In the current study, we aimed to assess the concentrations of the active metabolite of clopidogrel and its effect on platelet aggregation inhibition in patients receiving the originator drug in comparison with those receiving generic clopidogrel.

Materials and methods. We enrolled 22 healthy individuals without polymorphisms in the *ABCB1* gene and the allele variants *CYPC19*2* and *CYPC19*3*. All participants received a loading dose of clopidogrel (600 mg), followed by a maintenance dose of 75 mg for the next 3 days. On day 3, blood samples were obtained 1 h after drug administration to assess active metabolite concentrations using liquid chromatography with tandem mass spectrometry. In each participant, platelet aggregation was assessed with light transmission aggregometry after 5-µmol/L and 10-µmol/L adenosine diphosphate (ADP) stimulation. Assays were performed for the originator clopidogrel and 2 different generic groups.

Results. The mean ± standard deviation (SD) concentrations of active clopidogrel did not differ between the originator drug and 2 generic products with clopidogrel (12.7 ±5 pg/µL compared to 13.0 ±4 pg/µL compared to 14.4 ±4 pg/µL). Platelet aggregation inhibition after stimulation with 5 µmol/L and 10 µmol/L ADP was similar for all preparations.

Conclusions. In comparison with original clopidogrel, the use of its generic form does not affect the blood concentrations of the active metabolite or its antiplatelet effect.

Key words: *ABCB1*, clopidogrel active metabolite, *CYPC19*2*, *CYPC19*3*, clopidogrel bioequivalence

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Introduction

Although ticagrelor and prasugrel are increasingly widely used as antiplatelet therapy after coronary angioplasty, there is a large group of patients with indications for clopidogrel treatment. This population includes primarily symptomatic patients with chronic coronary syndrome and acute coronary syndrome (ACS), who are treated invasively, and who have contraindications to the use of novel antiplatelet drugs due to concomitant atrial fibrillation and antithrombotic treatment (particularly with non-vitamin K antagonist oral anticoagulants).[1,2] Several generic forms of clopidogrel are available on the market. However, it is unclear whether they are as effective in daily clinical practice as the originator drug. It has been shown that agreement between platelet function measurements is relatively poor in patients receiving original and generic clopidogrel bisulfate forms.[3] Thus, physicians may be cautious when routinely introducing generic clopidogrel bisulfate. On the other hand, risks of mortality, bleeding and drug discontinuation were not different between Plavix and generics.[4] The available evidence is therefore limited and does provide sufficient data on differences in efficacy or safety between branded and generic products.

Clopidogrel is a prodrug metabolized to its active form through complex biochemical processes in the liver.[5,6] Its absorption is regulated by glycoprotein P, a transport protein encoded by the *ABCB1* gene. Eight-five percent of the absorbed drug is transformed by carboxyl esterases into a major but inactive clopidogrel metabolite – a carboxylic acid derivative. Only 15% of the absorbed clopidogrel is transformed by cytochrome P450 (CYP) isoenzymes (*CYP2B6*, *CYP2C9*, *CYP2C19*, and *CYP3A4*) into a thiol metabolite, which is responsible for blocking adenosine diphosphate (ADP) binding to the platelet $P2Y_{12}$ receptor and ADP-induced platelet aggregation.

Objectives

In the current study, we aimed to assess the concentrations of clopidogrel active metabolite as well as its effect on platelet aggregation inhibition, in patients receiving the originator drug in comparison with those receiving generic clopidogrel. Active metabolite generation following clopidogrel administration is diminished by limited intestinal absorption (which may be influenced by the *ABCB1* gene polymorphism), as well as by functional variability in the activity of the CYP isoenzymes (which is influenced by single nucleotide polymorphisms (SNPs) in genes encoding the CYP isoenzymes).[7] Therefore, to exclude genetic variability that might affect drug concentration and activity, participants were assessed for the presence of the most common genetic polymorphisms that reduce the absorption (*ABCB1*) and activation (*CYPC19*2* and *CYPC19*3*) of clopidogrel.

Materials and methods

Study population

We enrolled 22 healthy, non-smoking participants, who provided written informed consent to be included in the study. The study protocol was approved by the bioethics committee of Wroclaw Medical University, Poland. None of the participants were carriers of polymorphisms in the *ABCB1* gene or the allele variants *CYPC19*2* or *CYPC19*3*. The study protocol was approved by the bioethics committee of Wroclaw Medical University, and it was also in line with the Helsinki Declaration.

Genetic studies

To identify genetic polymorphism, genetic material was extracted from 200 µL of whole-blood samples of each patient, using the High Pure PCR Template Preparation Kit (Roche Diagnostics, Warszawa, Poland). Using the ability of the DNA to bind with silica under certain conditions, the lysate was centrifuged in a mini-column containing the silica membrane, which was then rinsed twice with a washing buffer. Finally, a mini-column elution buffer was applied to the membrane to recover the purified DNA. Next, amplified polymerase chain reaction (PCR) was carried out with the use of 3 pairs of specific primers for *CYP2C19*3*, *ABCB1* (C3435C> T) and *CYP2C19*2*, as well as a Multiplex PCR Kit (Qiagen, Hilden, Germany), according to the manufacturer's instructions. A single nucleotide polymorphism of *CYP2C19*2*, *CYP2C19*3* and *ABCB1* was genotyped using a mini-sequencing technique, which is a modification of PCR. The SNaPshot Multiplex Kit (Applied Biosystems, Foster City, USA) was used for the analysis, according to the manufacturer's instructions. The mini-sequencing reaction was performed with specific primers designed to hybridize to the template, ending before the designated polymorphic site. Dideoxynucleotide triphosphates, or fluorescent-labeled terminators, were involved in the reaction. Product detection was performed with capillary electrophoresis, using a 3130 Genetic Analyzer (Applied Biosystems). The results were analyzed with the use of the GeneMapper ID v. 3.2 program (Applied Biosystems) against the internal GeneScan™ LIZ 120 standard.

Clopidogrel administration, blood collection and plasma preparation

At baseline, all participants received a loading dose of original clopidogrel (600 mg), followed by a maintenance dose of 75 mg for the next 3 days. On day 3, blood samples of 7.5 mL were drawn into collection tubes containing ethylenediaminetetraacetic potassium salt, to assess the concentrations of the drug active metabolite in patients' plasma. Samples were obtained 1 h after drug administration (C1h), taking into account the high active

metabolite concentration reported in previous pharmacokinetic studies.[7] Due to the irreversible nature of the receptor modification, subsequent clopidogrel preparations were analyzed after 1 week, which ensured a natural restoration of the platelet pool. In this crossover study, assays were performed separately for the originator drug – Plavix (Sanofi-Aventis, Paris, France) (P) and 2 different generic forms – Areplex (Adamed, Pieńków, Poland) (A) and Egitromb (Egis Pharmaceuticals, Budapest, Hungary) (E). Each subject received generic products and the reference product. All drugs contained clopidogrel bisulfate as the active substance.

Sample preparation

To stabilize the active clopidogrel metabolite, 2-bromo-3'-methoxyacetophenone (MPB) was added to the blood sample immediately after collection, in accordance with the procedure described by Takahashi et al.[8]

The MPB-derivatized clopidogrel active metabolite hydrochloride and [13C6]-clopidogrel carboxylic acid (internal standard) were purchased from Alsachim (Illkirch-Graffenstaden, France). Clopidogrel and clopidogrel carboxylic acid were obtained from the Pharmaceutical Research Institute (Warszawa, Poland). Liquid chromatography mass spectrometry (LC-MS) grade water, methanol, and acetonitrile were obtained from J.T. Baker (Deventer, the Netherlands). The formic acid (purity ≥98%), trichloroacetic acid (purity ≥99.5%) and MPB were purchased from Sigma-Aldrich (Poznań, Poland), while leucine-enkephalin was sourced from Waters (Warszawa, Poland).

Plasma concentrations of clopidogrel active metabolite hydrochloride, clopidogrel and clopidogrel carboxylic acid were quantified using stable-isotope dilution LC-MS, according to a modified method adapted from Karaźniewicz-Łada et al.[7] Briefly, a volume of 100 µL of either plasma sample or internal standard was combined with 20 µL of internal standard solution (500 pg/µL). Then, 400 µL of acetonitrile was added and vortexed for 5 min at 1100 rpm. After additional centrifugation, the supernatant was analyzed using LC with tandem MS (LC-MS/MS).

Liquid chromatography – tandem mass spectrometry

The LC-MS/MS analysis was conducted using the nanoACQUITY UPLC system, combined with a Xevo G2 QT of mass spectrometer (Waters). The analyzed compounds were separated in the HSS C18 column with membrane inline filter (Waters). The column temperature was set at 45°C. Mobile phase A consisted of 0.1% formic acid in water, while mobile phase B consisted of 0.1% formic acid in acetonitrile with an increasing gradient. The total run time of the method was 4 min, with a flow rate of 45 µL/min.

Mass spectra for the analyzed compounds were acquired in positive ion mode electrospray ionization. Data acquisition was performed with MassLynx Software (Waters), using the characteristic precursor and product ions. A quantitative analysis was also performed using QuanLynx software (Waters). We considered a range of 80–125% as an acceptance interval criterion for the clopidogrel mean concentration ratio for each tested product. For the measurement of clopidogrel active metabolite, a previously known measurement method was used, which was subject to detailed validation.[7]

Platelet aggregation

For each participant, platelet aggregation was assessed on day 3 of treatment with each preparation. Blood samples were obtained from a venous cannula into 2 tubes containing 0.109 mol/L of trisodium citrate, and centrifuged at room temperature (800 × g for 15 min) to collect platelet-rich plasma. The sample was re-centrifuged at 2400 × g for 15 min, and platelet-poor plasma was collected. Platelet reactivity was assessed within 2 h of collection, with light transmission aggregometry as developed by Born,[9] using a single-channel Chrono Log 560CA lumi-aggregometer (Chrono-Log, Haverton, USA). A platelet-poor plasma sample with 100% light transmission was used as a reference. Next, consecutive platelet-rich plasma samples (light transmission, 0%) were placed in cuvettes and stimulated with adenosine diphosphate (ADP; 5 µmol/L and 10 µmol/L). The results were expressed as percentage of the maximum platelet aggregation (MPA) within 6 min. Calculations and platelet aggregation curves were performed using the dedicated Agro-Link software (Chrono-Log). All reagents and laboratory equipment were purchased from Biogenet (Piaseczno, Polska). They were stored and used according to the manufacturer's instructions.

Cut-off MPA values higher than 46% and 67% were used to identify the lack of response to stimulation with 5 µmol/L and 10 µmol/L ADP, respectively.

Statistical analysis

The statistical analyses were performed using the STATISTICA v. 9.0 PL program (StatSoft Inc., Tulsa, USA). The variance homogeneity of each quantitative variable was determined using Levene's test. To compare the quantitative variables between groups, a one-way analysis of variance (ANOVA) was used. All hypotheses were verified at the statistical significance level $p \leq 0.05$.

Results

Demographic and clinical features of participants are presented in Table 1. The genetic analysis revealed that none of the participants were carriers of genetic polymorphisms responsible for reduced clopidogrel absorption and metabolism.

Table 1. Study population characteristics

Parameter	Study cohort
Age [years]	32 ±6.5
Sex (F/M)	8/14
Diabetes	0
Hypertension	0
Smoking	0
Hemoglobin [g/dL]	12.3 ±1.3
White blood cells [10^3/μL]	7.3 ±0.4
Creatinine [mg/dL]	0.9 ±0.4
Creatinine clearance [mL/min]	106.7 ±11.2
Body mass [kg]	62.7 ±16.3
BMI	24.6 ±4.2

SI conversion factors: to convert creatinine to μmol/L, multiply by 88.4. F – female; M – male; BMI – body mass index. Data are presented as mean ± standard deviation (SD).

We did not find any significant differences in the C1h concentrations of active clopidogrel between different preparations, specifically 12.7 ±5 pg/μL in group P, compared to 13.0 ±4 pg/μL in group A and 14.4 ±4 pg/μL in group E. This data is presented in Fig. 1.

Mean platelet aggregation inhibition values were similar for all drugs, without any significant differences, both after stimulation with 5 μmol/L ADP and 10 μmol/L ADP. Aggregation data are shown in Table 2.

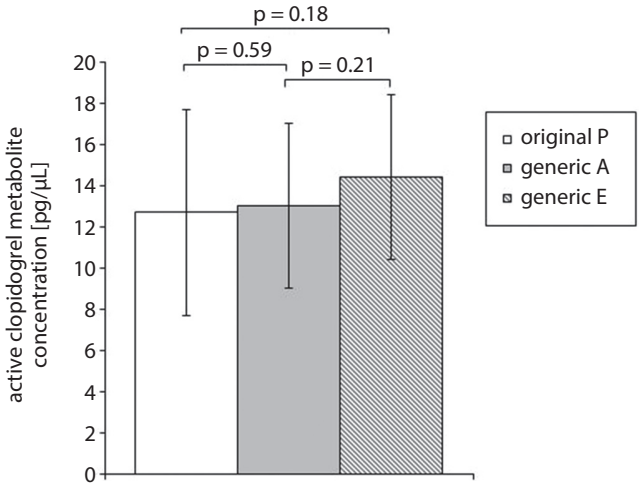

Fig. 1. Concentrations of clopidogrel active metabolite for original and generic drug

Table 2. Platelet aggregation values after ADP stimulation

Platelet aggregation	P	A	E
5-μmol/L ADP	34.5 ±9	35.0 ±7	36.6 ±8
10-μmol/L ADP	40.7 ±9	40.0 ±8	37.1 ±8

Data are presented as mean ± standard deviation (SD). ADP – adenosine diphosphate.

Discussion

Multiple lines of evidence suggest that insufficient active metabolite generation is the primary reason for variability in clopidogrel response and the lack of response where a negligible antiplatelet effect of clopidogrel is observed. High platelet reactivity to clopidogrel has been found to be associated with a significantly higher incidence of ischemic recurrence in patients undergoing percutaneous coronary intervention with stent implantation.[1,2,5] Therefore, the equal efficacy of generic drugs to that of the originator remains an important issue.

The cut-off values for defining clopidogrel non-responsiveness using aggregometry are often arbitrary.[10] The most important studies focusing on platelet activity used various concentrations of the $P2Y_{12}$ receptor inhibitor. The most common agonist in the largest studies was 5 μmol/L and 20 μmol/L ADP. In a group of 1069 patients with established chronic coronary syndrome undergoing percutaneous coronary intervention, Breet et al.[10] showed that an MPA of 42.9% or higher for 5 μmol/L ADP and of 64.5% or higher for 20 μmol/L ADP was associated with an increased risk of death, myocardial infarction, stent thrombosis, and ischemic stroke during a one-year follow-up. Gurbel et al.[11] reported a higher risk of cardiovascular events in a two-years follow-up in patients with an MPA higher than 46% and 59%, respectively. Cuisset et al.[12] revealed an elevated risk of stent thrombosis for an aggregation cut-off value higher than 67%. In 2010, Bonello et al.[13] published a consensus statement in which they proposed an ADP (5 μmol/L)-induced MPA of 46% as a cut-off value to identify high platelet reactivity. In our study, we accepted the recommended threshold of 46% for MPA induced by 5 μmol/L ADP, while for 10 μmol/L ADP, the cut-off value of more than 67% was used to identify an inadequate response to clopidogrel, as in the study by Cuisset et al.[12]

The quantitative assessment of the active form of clopidogrel in blood is a complex process, particularly due to the short half-life of the drug. High-performance liquid chromatography assays are not sensitive enough to measure clopidogrel levels in biological fluids after oral administration of therapeutic doses. The LC-MS/MS has been increasingly used because it can analyze test samples regardless of their purity in biological substances and measure drug concentrations in blood with high sensitivity and selectivity.[14,15] In our study, we used modified methods that allow for the stabilization of the active metabolite in blood.[8] The time of blood sampling, 1 h after drug administration, was chosen based on previous clopidogrel pharmacokinetic studies.[7] We decided to test each clopidogrel product after 1 week of treatment discontinuation, as it has been proven that complete recovery of platelet function can be seen 7 days after the last clopidogrel dose.[16]

We showed that the use of generic forms of clopidogrel does not significantly affect the blood concentrations of the active metabolite in healthy individuals with

the absence of the most common genetic polymorphisms (*ABCB1*, *CYPC19*2* and *CYPC19*3)*. Moreover, none of our participants showed a lack of response to antiplatelet treatment, expressed as a low rate of platelet aggregation inhibition. Therefore, the original clopidogrel and the tested generic forms can be considered equivalent.

Our findings are in line with previous studies that revealed similar efficacy of the original and generic forms of clopidogrel in patients with ACS and chronic coronary syndrome.[17,18] However, other studies have reported contradictory results.[19,20] An Italian study evaluated 1579 patients with ACS and found that a significantly higher proportion of patients treated with clopidogrel base had high platelet reactivity when compared with original clopidogrel. However, it is important to note that clopidogrel base is a generic preparation that differs from original clopidogrel, which is formulated using clopidogrel bisulfate. In contrast, in our study, both generic and original clopidogrel contained the same salt.

Limitations

Our study has several limitations. First, the study group was relatively small, and we did not assess the presence of other polymorphisms and other variables that might have affected drug concentrations in blood. However, our results indicate that the generic preparations of clopidogrel bisulfate tested have similar efficacy to original clopidogrel and thus may be used in clinical practice.

Conclusions

In comparison with original clopidogrel, the use of its generic form does not affect the blood concentrations of the active metabolite or its antiplatelet effect.

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References

1. Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: A systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J*. 2019;40(46):3757–3767. doi:10.1093/eurheartj/ehz732
2. Neumann FJ, Sousa-Uva M, Ahlsson A, et al; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87–165. doi:10.1093/eurheartj/ehy394
3. Jeong YH, Koh JS, Kang MK, et al. The impact of generic clopidogrel bisulfate on platelet inhibition in patients with coronary artery stents: Results of the ACCEL-GENERIC Study. *Korean J Inter Med*. 2010;25(2):154–161. doi:10.3904/kjim.2010.25.2.154
4. Caldeira D, Fernandes RM, Costa J, David C, Sampaio C, Ferreira JJ. Branded versus generic clopidogrel in cardiovascular diseases: A systematic review. *J Cardiovasc Pharmacol*. 2013;61(4):277–282. doi:10.1097/FJC.0b013e31827e5c60
5. Saiz-Rodríguez M, Belmonte C, Caniego JL, et al. Influence of CYP450 enzymes, CES1, PON1, ABCB1, and P2RY12 polymorphisms on clopidogrel response in patients subjected to a percutaneous neurointervention. *Clin Ther*. 2019;41(6):1199–1212.e2. doi:10.1016/j.clinthera.2019.04.037
6. Protasiewicz M, Szymkiewicz P, Kuliczkowski W, Mysiak A, Witkiewicz W. Modern antiplatelet therapy: Opportunities and risks. *Adv Clin Exp Med*. 2013;22(6):875–885. PMID:24431318
7. Karaźniewicz-Łada M, Danielak D, Burchardt P, et al. Clinical pharmacokinetics of clopidogrel and its metabolites in patients with cardiovascular diseases. *Clin Pharmacokinet*. 2014;53(2):155–164. doi:10.1007/s40262-013-0105-2
8. Takahashi M, Pang H, Kawabata K, Farid NA, Kurihara A. Quantitative determination of clopidogrel active metabolite in human plasma by LC-MS/MS. *J Pharm Biomed Anal*. 2008;48(4):1219–1224. doi:10.1016/j.jpba.2008.08.020
9. Born GV. Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature*. 1962;194:927–929. doi:10.1038/194927b0
10. Breet NJ, van Werkum JW, Bouman HJ, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA*. 2010;303(8):754–762. doi:10.1001/jama.2010.181
11. Gurbel PA, Antonino MJ, Bliden KP, et al. Platelet reactivity to adenosine diphosphate and long-term ischemic event occurrence following percutaneous coronary intervention: A potential antiplatelet therapeutic target. *Platelets*. 2008;19(8):595–604. doi:10.1080/09537100802351065
12. Cuisset T, Frere C, Quilici J, et al. Predictive values of post-treatment adenosine diphosphate-induced aggregation and vasodilator-stimulated phosphoprotein index for stent thrombosis after acute coronary syndrome in clopidogrel-treated patients. *Am J Cardiol*. 2009;104(8):1078–1082. doi:10.1016/j.amjcard.2009.06.007
13. Bonello L, Tantry US, Marcucci R, et al; Working Group on High On-Treatment Platelet Reactivity. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *J Am Coll Cardiol*. 2010;56(12):919–933. doi:10.1016/j.jacc.2010.04.047
14. Peer CJ, Spencer SD, VanDenBerg DA, Pacanowski MA, Horenstein RB, Figg WD. A sensitive and rapid ultra HPLC-MS/MS method for the simultaneous detection of clopidogrel and its derivatized active thiol metabolite in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2012;880(1):132–139. doi:10.1016/j.jchromb.2011.11.029
15. Karaźniewicz-Łada M, Danielak D, Teżyk A, Zaba C, Tuffal G, Główka F. HPLC-MS/MS method for the simultaneous determination of clopidogrel, its carboxylic acid metabolite and derivatized isomers of thiol metabolite in clinical samples. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2012;911:105–112. doi:10.1016/j.jchromb.2012.11.005
16. Weber AA, Braun M, Hohlfeld T, Schwippert B, Tschöpe D, Schrör K. Recovery of platelet function after discontinuation of clopidogrel treatment in healthy volunteers. *Br J Clin Pharmacol*. 2001;52(3):333–336. doi:10.1046/j.0306-5251.2001.01453.x
17. Ko DT, Krumholz HM, Tu JV, et al. Clinical outcomes of plavix and generic clopidogrel for patients hospitalized with an acute coronary syndrome. *Circ Cardiovasc Qual Outcomes*. 2018;11(3):11(3):e004194. doi:10.1161/CIRCOUTCOMES.117.004194
18. Hajizadeh R, Ghaffari S, Ziaee M, Shokouhi B, Separham A, Sarbakhsh P. In vitro inhibition of platelets aggregation with generic form of clopidogrel versus branded in patients with stable angina pectoris. *J Cardiovasc Thor Res*. 2017;9(4):191–195. doi:10.15171/jcvtr.2017.33
19. Marcucci R, Paniccia R, Gori AM, Gensini GF, Abbate R. Bioequivalence in the real world is a complex challenge: The case of clopidogrel. *J Am Coll Cardiol*. 2013;61(5):594–595. doi:10.1016/j.jacc.2012.10.020
20. Kovacic JC, Mehran R, Sweeny J, et al. Clustering of acute and subacute stent thrombosis related to the introduction of generic clopidogrel. *J Cardiovasc Pharmacol Ther*. 2014;19(2):201–208. doi:10.1177/1074248413510605