International Journal of Clinical and Experimental Medicine Research, 2024, 8(4), 587-592
https: //www.hillpublisher.com/journals/ijcemr/
ISSN Online: 2575-7970
ISSN Print: 2575-7989

Clinical Medication Analysis of Clopidogrel and Aspirin Guided by Medicine Gene Detection

Dingding Kang[1,*], Liushan Wei[2], Lianmei Xu[2], Liwei Yi[1]

[1]Affiliated Nanhua Hospital, Department of Pharmacy, Hengyang Medical School, University of South China, Hengyang 421001, Hunan, China.
[2]School of Pharmacy, Hengyang Medical School, University of South China, Hengyang 421001, Hunan, China.

How to cite this paper: Dingding Kang, Liushan Wei, Lianmei Xu, Liwei Yi. (2024) Clinical Medication Analysis of Clopidogrel and Aspirin Guided by Medicine Gene Detection. *International Journal of Clinical and Experimental Medicine Research*, 8(4), 587-592.
DOI: 10.26855/ijcemr.2024.10.009

Received: September 30, 2024
Accepted: October 28, 2024
Published: November 27, 2024

***Corresponding author:** Dingding Kang, Affiliated Nanhua Hospital, Department of Pharmacy, Hengyang Medical School, University of South China, Hengyang 421001, Hunan, China.

Abstract

Objective: Medicine gene detection is used to guide the clinical use of clopidogrel and aspirin, in order to improve the efficacy and safety of clinical treatment. **Methods:** A total of 214 patients who received clopidogrel and aspirin treatment at the Affiliated Nanhua Hospital of the University of South China from March 2022 to February 2023 were selected. The medicine genes were detected by pyrosequencing. The genotype distribution of each gene locus was tested by the Hardy-Weinberg equilibrium test with SPSS 26.0. The patients' clinical information was analyzed using the chi-square test and binary logistic regression. **Results:** Among the 130 patients using clopidogrel, gene loci CYP2C19*2 681 G>A and CYP2C19*3 636 G>A were detected. Among the 84 patients using aspirin, gene loci PEAR1 G>A and LTC4S A>C were detected. The gene frequency distribution of the gene loci all accorded with Hardy-Weinberg equilibrium law, which indicated the sample was group representation. 59.2% of patients had clopidogrel resistance, 72.6% of patients had aspirin resistance, and 33.3% of patients had a high risk of urticaria when using aspirin. However, there was no significant difference in clopidogrel and aspirin resistance or urticaria risk in relation to patients' clinical information ($P > 0.05$). The results of medicine gene detection could be used as an independent indicator to predict the efficacy and safety of using clopidogrel and aspirin, providing important guidance for the clinical use of medication. **Conclusion:** Medicine gene detection could promote individualized medication and improve the efficacy and safety of clinical treatment when guiding the use of clopidogrel and aspirin.

Keywords

Medicine gene detection; Clopidogrel; Aspirin; Individualized medication; Pyrosequencing

Introduction

Currently, the incidence of cardiovascular diseases is on the rise. The high mortality and treatment costs of cardiovascular diseases, such as coronary heart disease, have significantly impacted the quality of life [1]. Antiplatelet drugs, as first-line clinical medications for the treatment and prevention of cardiovascular diseases, demonstrate remarkable efficacy and are widely employed. Commonly used antiplatelet drugs in clinical practice include clopidogrel and aspirin. However, individual differences among patients may lead to resistance or bleeding risks during medication, ultimately resulting in poor efficacy and even adverse cardiovascular events [2]. Pharmacogenetic testing, as a crucial method in precision medicine, involves genotyping individuals prior to medication. This approach takes into account comprehensive factors that influence drug efficacy, providing precise guidance for individualized drug administration, thereby ensuring the effectiveness and safety of clinical medication. This study conducted pharmacogenetic testing analysis on patients using clopidogrel and aspirin, exploring the guiding role of pharmacogenetic testing in the clinical use of these drugs. The findings aim to provide a reference for the precise clinical medication of clopidogrel and aspirin in the future.

1. Data and Methods

1.1 Clinical data

214 patients were selected to receive treatment with Clopidogrel Hydrogen Sulphate Tablets (Sanofi Pharmaceutical Co., Ltd., National Medical Products Approval No. J20130083) and Aspirin Enteric-Coated Tablets (Bayer Healthcare Co., Ltd., National Medical Products Approval No. J20130087) at the Nanhua Affiliated Hospital from March 2022 to February 2023, and underwent relevant genetic testing. Collect the patient's age, gender, smoking history, drinking history, diabetes, hypertension, hyperlipidemia, and medication in the hospital information management system.

1.2 Pharmacogenetic testing methods

The drug-related gene loci in patient blood samples were tested using the pyrophosphate sequencing detection method. The instrument used was the pyrophosphate sequencer (PYROSEQ-E16) (Wuhan FIRST Biotechnology Co., Ltd.), and the reagent used was the universal sequencing reaction kit. The experimental operation was strictly carried out according to the instructions.

1.3 Analysis of gene polymorphisms

Using the Hardy-Weinberg equilibrium law and chi-square test to verify the independence of allele distribution, $P>0.05$ indicates compliance with the Hardy-Weinberg equilibrium law and significant difference.

1.4 Statistical analysis

Using SPSS 26.0 statistical software, binary logistic regression analysis was performed on the clinical data and drug genetic testing results of patients, with $P < 0.05$ indicating statistical significance.

2. Results

2.1 Genotype and phenotype

2.1.1 Clopidogrel

There are 59 individuals with CYP2C192 genotype GG, representing a frequency of 45.4%, 64 with genotype GA, accounting for 49.2%, and 7 with genotype AA, representing 5.4%. The frequency of the G allele is 70.0%. Additionally, there are 120 individuals with CYP2C193 genotype GG, constituting a frequency of 92.3%, and 10 with genotype GA, representing 7.7%. The frequency of the G allele stands at 96.2%. According to the chi-square test results, all P-values are greater than 0.05, indicating that the sample adheres to Hardy-Weinberg equilibrium and is representative of the population. The CYP2C192 and CYP2C193 alleles can lead to three phenotypes in the population: slow metabolizer, intermediate metabolizer, and fast metabolizer. Based on the genotype results, there were 11 cases of slow metabolizer type in this study, accounting for 8.4%, 66 cases of intermediate metabolizer type, representing 50.8%, and 53 cases of fast metabolizer type, constituting 40.8%. Please refer to Table 1 for further details.

2.1.2 Aspirin

PEAR1 genotype: 23 individuals with GG, accounting for 27.4%, 46 individuals with GA, accounting for 54.8%, and 15 individuals with AA, accounting for 17.9%. The frequency of the G allele is 54.8%. LTC4S genotype: 56 individuals with AA, accounting for 66.7%, 26 individuals with AC, accounting for 31.0%, and 2 individuals with CC, accounting for 2.4%. The frequency of the A allele is 82.2%. According to the chi-square test results, all P-values are greater than 0.05, indicating that the sample adheres to Hardy-Weinberg equilibrium and is representative of the population. Mutations in the PEAR1 allele can lead to aspirin resistance in the population. Based on the genotype results, 61 individuals in this study are at risk of aspirin resistance, accounting for 72.6%. Mutations in the LTC4S allele increase the risk of urticaria in individuals taking aspirin. According to the genotype results, 28 individuals in this study were found to have an increased risk of developing urticaria when using aspirin, accounting for 33.3% (please see Table 1).

Table 1. Distribution of genotype frequencies related to clopidogrel and aspirin

Drug	Gene	Locus	Genotype	No.	Percent (%)	χ^2	*P*
Clopidogrel (n = 130)	CYP2C19*2	681 G > A	GG	59	45.4	4.33	0.11
			GA	64	49.2		
			AA	7	5.4		
	CYP2C19*3	636 G > A	GG	120	92.3	0.23	0.89
			GA	10	7.7		
Aspirin (n = 84)	PEAR1	106 G > A	GG	23	27.4	0.93	0.68
			GA	46	54.8		
			AA	15	17.9		
	LTC4S	444 A > C	AA	56	66.7	0.39	0.82
			AC	26	31.0		
			CC	2	2.4		

2.2 Clinical data statistics

The average age of 214 patients was (61.98 ± 11.21) years, with 153 being male (71.50%) and 61 female (28.50%). Among those treated with clopidogrel, there were 130 cases, with an average age of (61.54 ± 11.04) years, including 95 males (73.1%) and 35 females (26.9%). For aspirin, 84 cases were treated, with an average age of (62.65 ± 11.49) years, including 58 males (69.1%) and 26 females (30.9%).

This study conducted CYP2C192 and CYP2C193 allele testing on 130 patients taking clopidogrel. Among the population, 50.8% were mainly of the intermediate metabolism (IM), followed by 41.8% of the extensive metabolizer (EM) and 8.4% of the poor metabolizer (PM). Using SPSS26.0 software to conduct a binary logistic regression analysis, the statistical results showed that there was no statistical difference between the risk factors of cardiovascular diseases such as age, sex, smoking, drinking, hypertension, diabetes, hyperlipidemia, and the drug-gene detection results of clopidogrel metabolism speed ($P > 0.05$) (please see Table 2).

Table 2. Comparison of clinical data between clopidogrel resistance and normal patients [$\bar{x} \pm s$, n (%)]

Items	EM (n = 53)	IM (n = 66)	PM (n = 11)	P
Age	61.09 ± 11.70	60.68 ± 10.72	62.09 ± 9.45	0.527
Male/n (%)	37 (69.8)	50 (75.6)	7 (63.6)	0.854
Smoking history/n (%)	15 (28.3)	27 (40.9)	3 (27.3)	0.382
Drinking history/n (%)	4 (7.5)	8 (12.1)	2 (18.2)	0.321
Diabetes/n (%)	14 (26.4)	22 (33.3)	4 (36.4)	0.138
Hypertension/n (%)	33 (62.3)	44 (66.7)	4 (36.4)	0.667
Hyperlipemia/n (%)	14 (26.4)	24 (36.3)	3 (27.3)	0.290

This study conducted PEAR1 and LTC4S allele testing on 84 patients taking aspirin. Among them, 61 were at risk of aspirin resistance (AR), accounting for 72.6%, and 28 were at an increased risk of urticaria when using aspirin, accounting for 33.3%. Using SPSS26.0 software to conduct a binary logistic regression analysis, the statistical results indicated that there were no significant statistical differences between the risk factors of cardiovascular diseases, such as age, gender, smoking, alcohol consumption, hypertension, diabetes, hyperlipidemia, and the risks of aspirin resistance and urticaria indicated by drug-gene testing ($P > 0.05$) (please see Table 3 and Table 4).

Table 3. Comparison of clinical data between aspirin resistance and normal patients [$\bar{x} \pm s$, n (%)]

Items	Aspirin resistance (n = 61)	Normal (n = 23)	*P*
Age	63.9 ± 11.2	59.5 ± 11.9	0.058
Male/n (%)	44 (72.1)	14 (60.1)	0.410
Smoking history/n (%)	20 (32.8)	7 (30.4)	0.473
Drinking history/n (%)	6 (9.8)	2 (8.7)	0.714
Diabetes/n (%)	22 (36.1)	4 (17.4)	0.305
Hypertension/n (%)	36 (59.0)	9 (39.1)	0.603
Hyperlipemia/n (%)	16 (26.2)	7 (30.4)	0.670

Table 4. Comparison of clinical data between high-risk and low-risk patients with aspirin induced urticaria [$\bar{x} \pm s$, n (%)]

Items	High-risk (n = 56)	Low-risk (n = 28)	*P*
Age	62.2 ± 12.3	63.6 ± 9.8	0.198
Male/n (%)	35 (62.5)	23 (82.1)	0.280
Smoking history/n (%)	14 (25.9)	13 (46.6)	0.423
Drinking history/n (%)	4 (7.1)	4 (14.3)	0.804
Diabetes/n (%)	19 (33.9)	7 (25.0)	0.751
Hypertension/n (%)	30 (53.6)	15 (53.6)	0.796
Hyperlipemia/n (%)	15 (26.8)	8 (28.6)	0.540

3. Discussion

3.1 Clopidogrel-related medicine gene detection

Clopidogrel is a prodrug, and CYP2C19 plays a crucial role in the two-step metabolic process that converts clopidogrel into its active metabolites [3, 4]. Studies have indicated that CYP2C19 gene polymorphism is the primary genetic factor contributing to clopidogrel resistance [5]. Patients carrying CYP2C19 2 and 3 alleles may exhibit reduced conversion of clopidogrel to its active metabolites, resulting in decreased platelet inhibition and an elevated risk of cardiovascular adverse events [6, 7].

The genetic testing results of clopidogrel in 130 patients in this study revealed that 40.8% were CYP2C19 fast metabolizers, 50.8% were CYP2C19 intermediate metabolizers, and 8.4% were CYP2C19 slow metabolizers. This finding aligns with the reported frequency distribution of CYP2C192 and CYP2C193 in Asians, which ranges from 29% to 35% and 2% to 9%, respectively [8, 9]. For patients with intermediate and slow metabolisms, caution should be exercised regarding clopidogrel resistance when administering clopidogrel. This suggests that over half of the normal population may develop resistance to clopidogrel, thereby affecting its therapeutic efficacy. Through statistical analysis of the clinical data from the study population, it was found that the distribution of CYP2C19 phenotypes was not associated with the patients' age, gender, smoking history, alcohol consumption history, or medical history ($P > 0.05$). This indicates that the drug-gene testing results of CYP2C19 can serve as an independent reference indicator for the clinical use of clopidogrel. These results underscore the necessity of drug genetic testing for users of clopidogrel. The "Technical Guidelines for Gene Detection of Drug Metabolizing Enzymes and Drug Action Targets (Trial)" implemented in 2015 [10] suggests that individuals with CYP2C19 fast metabolism should effectively use clopidogrel and can do so routinely; individuals with CYP2C19 intermediate metabolism may experience reduced efficacy of clopidogrel and are advised to switch to prasugrel or ticagrelor; individuals with CYP2C19 slow metabolism may exhibit poor efficacy when using clopidogrel and are recommended to switch to prasugrel or ticagrelor.

3.2 Aspirin-related medicine gene detection

PEAR1, as a membrane protein involved in platelet contact activation and aggregation, plays a crucial role in the platelet aggregation process [11]. Studies have indicated a strong correlation between the genetic polymorphism of PEAR1 and ADP-induced platelet aggregation in Chinese CHD patients after aspirin administration. Variations in PEAR1 can predict cardiovascular risk, and its genetic polymorphism is closely linked to the efficacy of aspirin [12].

Reports on the LTC4S gene [13-15] indicate that when the A site of the LTC4S gene mutates to C, the synthesis of leukotrienes in the human body significantly increases. Coupled with the effect of aspirin, this ultimately leads to an increase in leukotriene concentration in the human body, elevating the risk of urticaria in aspirin users. Therefore, the variation of the LTC4S gene locus is closely related to aspirin-induced urticaria. Patients undergoing LTC4S gene testing before using aspirin can provide a reference for the safe clinical use of aspirin, which is necessary for today's era of advocating individualized medication.

According to Table 1, there were 15 cases of the AA type of the aspirin PEAR1 gene, representing a mutation frequency of 17.9%, and 46 cases of the GA type, with a mutation frequency of 54.8%. There were 2 individuals with the CC genotype of LTC4S, accounting for a frequency of 2.4%, and 26 individuals with the AC genotype, representing a frequency of 31.0%. Mutations in the PEAR1 allele can lead to aspirin resistance in the population, reduce the efficacy of aspirin, and increase the risk of cardiovascular bleeding. Mutations in the LTC4S allele increase the risk of urticaria in individuals taking aspirin. For patients with PEAR1 and LTC4S gene mutations, attention should be paid to the risk of developing aspirin resistance and urticaria, and medication regimens should be adjusted in a timely manner. Through statistical analysis of the clinical data of the study population, it was found that the distribution of PEAR1 and LTC4S phenotypes in this study population was not related to the patient's age, gender, smoking history, alcohol consumption history, and medical history ($P > 0.05$), indicating that the drug-gene testing results of PEAR1 and LTC4S can serve as independent reference indicators for the clinical use of aspirin.

4. Conclusion

In summary, numerous factors influence the treatment of cardiovascular diseases. Genetic testing for clopidogrel and aspirin can serve as independent reference indicators for clinical treatment. Utilizing genetic testing to guide the clinical administration of clopidogrel and aspirin can facilitate individualized and precise drug administration, thereby enhancing the efficacy and safety of clinical medication. Hence, genetic testing merits promotion in clinical applications. This study also possesses certain limitations, primarily due to the limited number of collected samples, which may introduce certain biases into the research findings. Moving forward, we will continue to collect clinical samples and integrate them with clinical research analysis, aiming to establish a foundation for precise treatment of cardiovascular diseases.

References

[1] Goldfarb MJ, Bechtel C, Capers Q 4th, et al. Engaging Families in Adult Cardiovascular Care: A Scientific Statement from the American Heart Association. Journal of the American Heart Association. 2022;11(10):e025859.

[2] Pereira NL, Rihal C, Lennon R, et al. Effect of CYP2C19 genotype on ischemic outcomes during oralp2y 12 inhibitor therapy. JACC-Cardiovascular Interventions. 2021;14(7):739-750.

[3] Lee YC, Liao YC, LIN C J, et al. Baseline P2Y12 reactivity, kidney function, and CYP2C19 genotype determine clopidogrel responsiveness in acute stroke. Scientific Reports. 2023;13(1):8085.

[4] Kazui M, Nishiya Y, Ishizuka T, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. Drug Metabolism & Disposition the Biological Fate of Chemicals. 2010;38(1):92-99.

[5] Patel S, Arya V, Saraf A, et al. Aspirin and Clopidogrel Resistance in Indian Patients with Ischemic Stroke and its Associations with Gene Polymorphisms: A Pilot Study. Annals of Indian Academy of Neurology. 2019;22(2).

[6] Paré G, Mehta SR, Yusuf S, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. New England Journal of Medicine. 2010;363(18):1704-1714.

[7] Lima JJ, Thomas CD, Barbarino J, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2C19 and proton pump inhibitor dosing. Clinical Pharmacology & Therapeutics. 2021;109(6):1417-1423.

[8] Scott SA, Sangkuhl K, Stein CM, et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clinical Pharmacology & Therapeutics. 2013;94(3):317-323.

[9] Hokimoto S, Akasaka T, Tabata N, et al. Impact of CYP2C19 polymorphism on residual platelet reactivity in patients with coronary heart disease during antiplatelet therapy. Thrombosis Research. 2015;135(6):1081-1086.

[10] The health and family planning commission of the People's Republic of China. Summary of the technical guidelines for column measurement of drug metabolism enzymes and drug action target genes (trial). Practical Organ Transplantation Electronic Journal. 2015;3(5):257-267.

[11] Huang H, Zhang S, Du H, Guo Y, Zheng H. Effect of Clopidogrel combined with aspirin in the treatment of acute progressive cerebral infarction: A retrospective single-center analysis. Pakistan Journal of Medical Sciences. 2024;40(5):891-895.

[12] Yao Y, Tang XF, Zhang JH, et al. Association of PEAR1 genetic variants with platelet reactivity in response to dual antiplatelet therapy with aspirin and clopidogrel in the Chinese patient population after percutaneous coronary intervention. Thrombosis Research. 2016;141:28-34.

[13] Hui Z, Lin S, Hui XL, et al. Gene polymorphism of aspirin-induced urticaria in children with Kawasaki disease. Frontiers in Pediatrics. 2019;7:505-505.

[14] Mastalerz L, Setkowicz M, Sanak M, et al. Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. Journal of Allergy and Clinical Immunology. 2004;113(4):771-775.

[15] Mastalerz L, Setkowicz M, Sanak M, et al. Familial aggregation of aspirin-induced urticaria and leukotriene C synthase allelic variant. British Journal of Dermatology. 2006;154(2):256-260.