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Pharmacogenomics and its impact on individual response to cardiovascular medications

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ABSTRACT

Introduction: the discovery of the human genome set the tone for the development of pharmacogenomics, which has given promising results that invite the prescription of individualized medicine with the aim of optimizing the response to treatment and reducing the adverse effects that could occur, with For these purposes, it is essential to carry out this study. Objective: To describe the impact of pharmacogenomics on individual response to cardiovascular medications. Methods: 52 articles were identified, of which 20 were included. They came from academic search engines such as PubMed, MedLine, Ovid, ResearchGate and Google Scholar. Development: Pharmacogenetic studies are based on the investigation of candidate genes selected for their biological importance, either in kinetics or for their relationship in pharmacological action; The ultimate goal is to identify individuals at risk of experiencing adverse effects or likely to be resistant to treatment. Conclusions: the success of modern medicine is partly the result of highly effective pharmacological treatments. In turn, the integration of pharmacogenomics into cardiovascular clinical practice has the potential to make significant contributions to medicine and improve clinical outcomes to reduce side effects in patients with cardiovascular diseases.

Keywords: Cardiology, Cardiovascular diseases, Pharmacogenetics, Cardiovascular drugs, Human genome, Pharmacotherapy.

Introduction

The discovery of the human genome set the pace for the development of pharmacogenomics, which has yielded promising results that enable personalized drug prescriptions to optimize treatment response and reduce potential side effects. Therefore, it is important to understand the advances in pharmacogenomics for common clinical conditions such as cardiovascular, thromboembolic, neuropsychiatric, and gastrointestinal diseases, to name a few(1).

Friedrich Vogel was the first to use the term pharmacogenetics in 1959, but it was not until 1962 when pharmacogenetics was defined as the study of genetic variations that cause variability in response to drugs(1).

Pharmacogenomics is an important tool for personalizing cardiovascular treatments and optimizing drug efficacy and safety based on an individual's genetics. This can help improve clinical outcomes and reduce side effects in patients with cardiovascular disease(2).

Genotypic, phenotypic, or both, characterization of key enzymes in the metabolism of drugs used in the treatment of these diseases will be useful for therapeutic selection and improvement of clinical outcome in the affected patient(2).

The pharmacological effects of the most commonly prescribed drugs are the result of a series of pharmacokinetic processes, which determine the amount of drug reaching the biophase, and pharmacodynamics, related to the effectiveness of the drug's interaction with its receptor. The variability in the expression and function of the various enzymes involved in these processes constitutes the core of pharmacogenomic studies(2).

It is clear that this analysis does not explain all the variability in therapeutic response, but rather is based on differences determined by sex, age, diet, comorbidities, environmental factors, and drug interactions. Pharmacogenomics can facilitate the identification of biomarkers useful for selecting the appropriate drug, the appropriate dose, the optimal timing of treatment, or the prevention of side effects(3).

Possible genetic variants include deletions, insertions, or multiplications, which may involve relatively large portions of the cell's deoxyribonucleic acid (DNA), although the most common target of pharmacogenetic assays are single nucleotide polymorphisms (SNPs)(4).

The sequencing of the human genome has revealed more than 10 million SNPs, specific sites where a change in the nucleotide sequence occurs. Of these, only a minority appear to have any influence on drug kinetics or dynamics. Therefore, the phases of pharmacogenomic study can range from purely genetic aspects to the identification of SNPs with clinical significance or, conversely, the establishment of specific nucleotide sequences based on the identification of individuals with particular behaviors related to drug metabolism.

Genes encoding metabolizing proteins may have different allelic variants, some of which have different influences on the level of expression of their products(5).

Over the past decade, knowledge of pharmacogenomics related to cardiovascular drugs has increased significantly. Advanced methods include the pharmacogenomics guide for anticoagulant therapy with

dicoumarol, while others attempt to define their place in therapy, such as the pharmacogenomics of clopidogrel and statins(5).

The relative importance of pharmacogenetic analysis in explaining the study of variability in response to cardiovascular drugs has been shown to be insufficient to justify its incorporation into routine practice. Based on the above, the objective of this research is to describe the impact of pharmacogenomics on the individual response to cardiovascular medications.

Methods

A review article was prepared using the keywords: Cardiology; Cardiovascular diseases; Pharmacogenetics; Cardiovascular drugs; Human genome. Fifty-two articles were identified from academic medical search engines such as PubMed, MedLine, Ovid, ResearchGate, and Google Scholar, of which 20 were included. The inclusion criteria for the review were articles published between 2018 and 2024, with full-text availability, and the search was limited to English and Spanish. Those not focused on the topic to be addressed in the objective were excluded.

Development

Most pharmacogenomic advances in cardiovascular therapy are currently in the validation and demonstration phase of potential clinical utility. Common challenges in genomic research across therapeutic areas include problems with the original study design, the risk of insufficient sample size, a lack of reproducibility constraints, and underlying phenotypic heterogeneity in the population. Major advances in this direction will come from the use of next-generation sequencing technologies focused on faster turnaround times, clearer phenotypic definitions, and multicenter collaboration(6), (7).

However, it is important to remember that for most drugs, individual differences are not important in predicting response, and this makes sense from an evolutionary perspective. As with dicoumarol anticoagulants, analysis of genetic variation in combination with individual clinical factors (e.g., body weight, body surface area, age, comorbidities) improves the accuracy of estimates(8).

The success of modern medicine is partly the result of highly effective drug treatments. It is well known that each person responds differently to drug therapy, and no medication is 100% effective for all patients. Therefore, the range of responses to drug treatment varies, as some people may achieve the desired effect, while others lack therapeutic results and experience side effects(9).

The existence of interindividual heterogeneity in drug response affects both efficacy and toxicity and may be mediated by changes in drug pharmacokinetics and pharmacodynamics. These mechanisms of variation are determined by the interaction of genetics and the environment. The contribution of each factor varies according to the drug(10).

Pharmacogenetic studies are based on the investigation of candidate genes selected for their biological importance, either in kinetics or for their relationship to pharmacological action; the ultimate goal is to identify individuals at risk of experiencing adverse effects or likely to be resistant to treatment(11).

Warfarin and acenocoumarol are the most widely prescribed coumarin-derived oral anticoagulants worldwide, and are indicated in patients with venous thromboembolism, atrial fibrillation, and mechanical heart valves. Although the mechanism of action of these drugs is similar, there are some important differences in their pharmacokinetics, for example, warfarin has lower activity than acenocoumarol and higher ADRs(12).

Genetic variation in the lipid-lowering efficacy of statins has been extensively investigated and more than 40 candidate genes have been described.

solute carrier organic anion transporter family member 1B1) has been identified as a relevant pharmacogenomic factor , particularly the genetic variants rs4363657 and rs4149056 (521T C, V174A; SLCO1B1*5), mainly related to statin-induced muscle toxicity(12), (13).

Studies have reported a strong association between the variant and the presence of severe myopathy. The association between the genetic variant and adverse reactions to statins has been particularly demonstrated with simvastatin(13), (14).

Clopidogrel is a thienopyridine commonly used to treat acute coronary syndrome (ACS). It is the drug of choice for preventing thrombosis after percutaneous coronary intervention (PCI) with coronary stenting(14).

Clopidogrel is a prodrug that requires the presence of P-glycoprotein encoded by the multidrug resistance 1 (MDR1) or ATP-binding cassette subfamily B member 1 (ABCB1) genes for absorption. Once the molecule is absorbed, it is converted into the active metabolite in two steps. In the first step, 2-oxoclopidogrel is produced by CYPs 2C19, 2B6, and 1A2, while the production of active thiols depends on the activity of CYPs 2C19, 3A4/5, 2B6, and 2C9.17. Finally, this compound inhibits the adenosine diphosphate (ADP) receptor P2Y12 expressed by platelets. This generally promotes platelet degranulation and the expression of GP IIb/IIIa receptors on their surface. Only 15% of the prodrug is converted into the active metabolite and the remainder is hydrolyzed by esterases(14), (15).

Responses to clopidogrel vary widely from person to person, with 4% to 30% experiencing lack of response 24 hours after drug administration, depending on how drug efficacy is assessed(15).

Given the magnitude of such variability, several studies(16), (17)have identified groups of patients who present platelet aggregation that is different from that of other subjects with the same clinical symptoms when taking normal doses of clopidogrel. On the other hand, other authors have suggested that this leads to an increased risk of cardiovascular events(13), (14), (18).

In the authors' view, it is important to note that this variability depends not only on genetic determinants, but also on factors such as age, smoking, body mass index, comorbidities such as diabetes mellitus, certain dyslipidemias, and the presence of drug interactions.

Angiotensin-converting enzyme inhibitors (ACE inhibitors) are the current first-line drug class for the treatment of hypertension. However, the insertion-deletion polymorphism (rs4646994) is significantly associated with plasma ACE concentrations, although the usefulness of this determination has not been confirmed in clinical trials(15).

Furthermore, the M235T mutation in the AGT gene encoding angiotensinogen is associated with the risk of stroke and acute myocardial infarction in patients receiving ACE inhibitors, and its relevance should be confirmed in further studies. A combination of 3 polymorphisms (2 in the angiotensin II type I receptor gene and one in the BKI gene of the bradykinin type I receptor) allowed to adequately predict the response and the risk of toxicity in the use of perindopril(16).

In the case of beta-blockers, the Ser49Gly polymorphism of the β-1 receptor was associated with an increase in the receptor process and allowed the identification of patients with dilated cardiomyopathy with a higher risk of mortality at 5 years of treatment with low doses. The Arg389Gly polymorphism of the same receptor present in homozygosis was significantly associated with an improvement in the ejection fraction, a reduction in the risk of hospitalization and mortality, in patients treated with beta-blockers(17).

The effect of this polymorphism on blood pressure reduction is controversial. Genetic polymorphisms and mutations that are strongly associated with the effects of antihypertensive drugs remain unclear. Most results from pharmacogenomic or pharmacogenetic studies are not validated or cannot be reproduced in other studies(18).

Despite a growing number of studies demonstrating a link between drug responses and drug metabolism genes (pharmacogenomics), most of this type of cardiovascular research is still in its infancy and researchers have struggled to identify and verify relationships(19). This may be primarily due to the patient population and their phenotype, or the difficulty in ensuring an adequate sample size.

The establishment of a research consortium will overcome these limitations and advance research standardization; it will also facilitate better utilization of relevant funding, the conduct of large-scale studies, and pharmacogenomics-related assessments in different ethnic groups. Meta-analyses validate the associations found, establish minimum standards of evidence for genetic associations, and propose clinical consensus guidelines(20).

Continued research and development of clinical trials evaluating the impact of pharmacogenomics on individual response to cardiovascular medications is necessary to improve personalized healthcare.

Conclusions

The integration of pharmacogenomics into cardiovascular clinical practice has the potential to make significant contributions to medicine and improve clinical outcomes by reducing side effects in patients with cardiovascular disease .

AUTHORSHIP CONTRIBUTION

CADBM: conceptualization, research, methodology, project management, validation, original draft writing, review, editing.

YER: conceptualization, research, methodology, validation, writing of the original draft, review, editing.

SRLA: conceptualization, research, methodology, validation, writing of the original draft, review, editing.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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