Pharmacogenetics of Cardiovascular Diseases "Medical Horizons"

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Pharmacogenetics is a study of the effect of genetic variation on drug therapy. Usually, it describes the influence of single genes on drug response while pharmacogenomics describes a larger number of genes, up to whole genome.
Among cardiovascular diseases, variations in genes affect the pharmacodynamics and pharmacokinetics of the drug may affect on pharmacological response, as follow:

Hypertension

There are five antihypertensive drug classes recommended for treatment of hypertension. Many studies reported that there is a variation in controlling blood pressure however hypertensive patients on drug therapy. At present, Beta1-adrenoreceptor (ADRB1) polymorphisms (Arg389Gly) represent the only example with potential for near term translation to practice. It has been reported that Arg389 homozygous genotype has the greatest blood lowering. Arg389 form of Beta1-adrenoreceptor couples more efficiently to G-protein, resulting in enhanced signal transduction. So, beta-blockers provide superior reduction in adverse cardiovascular events for patients with Arg389 genotype.

Dyslipidemia

Despite widespread use of drugs to correct lipoprotein abnormalities, there is tremendous variability in drug response in terms of both lipoprotein and inflammatory protein changes. Most of the studies tried to investigate the pharmacogenetic of HMG-CoA reductase inhibitors (statins). Candidate genes in statin pharmacogenetics involve CYP3A4 and CYP3A5 enzymes, organic anion transporters, cholesterol synthesis and lipoprotein metabolism. In addition, endothelial nitric oxide synthase gene (eNOS) where investigated to study the pleiotropic effect of statin (decreasing of platelet aggregation). Apolipoprotein E gene (APOE) was associated with variable LDL responses to statins. Also, myopathy side effect of statin was associated with NOS3 polymorphisms. Pharmacogenetic studies of statin pleiotropic effect are limited, and replication of significant genetic association is inconsist.

Coronary artery disease and stroke

Antiplatelet, anticoagulant and thrombolytic drugs are essential to prevent and treat coronary heart disease and stroke. 5-60% of patients on aspirin and 4-30% of patients on clopidogril fail to exhibit adequate inhibition of platelet. The glycoprotein IIIA PIA polymorphism (Leu33Pro) is the most commonly studied candidate for aspirin or clopidogrel resistance, although the data are conflicting. Numerous studies have documented that the VKORC1 and CYP2C9 variants are important determinant of warfarin therapy. Indeed, the US food and Drug administration (FDA) changed the warfarin label to indicate the physicians should consider lower initial doses in certain genetically defined populations. Additionally, clinical monitoring of platelet aggregation may eventually obviate the need for genotyping.

Heart Failure

Patients routinely receive a minimum of three or four drugs, including an ACE inhibitor, a beta-blocker, a diuretic, and digoxin. Vasodilators and spironolactone are added if the the syndrome progresses. It is reported that insertion/deletion (I/D) polymorphisms in ACE gene affect on ACE inhibitors. The D allele has been associated with increased mortality, which high-dose, but not at low dose. Also, it is reported that beta-blockers diminished D allele risk. Also, as it is metioned above (in hypertension part), Arg389Gly polymorphisms affect on Beta1-adrenoreceptor and hence on Beta-blocker drugs. Bucindolol significantly lowered the death among Arg389 patients. Additionally, in the near future, ADRB1 and ADRA2C genotypes may help guide therapy with bucindolol, if not beta-blocker therapy in general.

Dysrythmia

There is a fact that genetic variation affects on drug induced QT interval and increase the life-threatening ventricular dysrhythmia. Drug-induced QT prolongation and subsequent arrhythmia have been described for antihypertensives, antihistamines, flouroquinolone, antipsychotic agents and antiarrhythmia and others. In general, genes associated with congenital long QT syndromes have also been associated with drug-induced QT prolongation.

Variations in genes that regulate potassium and sodium channels (KCNQ1/ KvLQT1; KCNH2/ HERG; SCN5A) have been identified to occur in a subset of patients who experience drug-induced QT prolongation. In addition, drug metabolism enzyme polymorphisms e.g. CYP2D6, CYP2C9, CYP2C19 and CYP3A as well as clinical variables e.g. sex, renal function and serum electrolyte may be considered when stratifying patients risk.

Pharmacogenetics of Warfarin

Warfarin is an oral anticouaglant coumarin derivative which is still the only oral anticoaglunt available for long-term use in United States. It is indicated for prevention and treatment of venous thromboembolism. Also, it is used for long-term anticoagulation in patients with atrial arrhythmias and mechanical heart valves. Warfarin differs from most of other drugs in that the dosage required to achieve a desired therapeutic effect varies greatly among individuals. This variability can lead to therapeutic failure and resulting in thrombosis formation. This variation in warfarin response could be acquired or hereditary or both of them. Hereditary factor is caused by genetic variations in genes affect on warfarin metabolism (pharmacokinetics variations) or in genes affect of thrombosis formation (pharmacodynamics variations). Pharmacokinetics variation is due mainly to single nucleotide polymorphisms in gene encodes Cytochrome P450 2C9 (CYP2C9), which metabolize warfarin to inactive metabolite. It is reported that people who carry multiple copies of CYP2C9 were associated with higher than normal activity and reduced warfarin plasma concentration. In addition, it is reported that CYP2C9*2 and CYP2C9*3 genotype are independent predictors of low warfarin dose requirement. On the other hand, warfarin pharmacodynamics is inhibition of vitamin K 2,3-epoxide reductase complex, subunit 1 (VKORC1). It is reported that a heterozygous point mutation in the VKORC1 gene, which change amino acid sequence (Va129Leu, Va145Ala, and Arg58Gly), decreased the affinity of warfarin binding to VKORC1 and resulted in decreased warfarin response. So, higher warfarin dose is recommended for patients with these genetic variations. As mentioned above, the US food and Drug administration (FDA) changed the warfarin label to indicate the physicians should consider lower initial doses in

certain genetically defined populations.

Pharmacogenetics of Clopidogrel

Clopidogrel is an oral, thienopyridine class antiplatelet agent used to inhibit blood clots in coronary artery disease. Clopidogrel is now the standard of care in patients with acute coronary syndromes and those undergoing percutaneous coronary intervention. It is an inactive prodrug that requires in vivo conversion in the liver by the cytochrome P450 3A4 enzyme system to an active metabolite and acts via irreversible antagonism of the platelet P2Y12 adenosine diphosphate (ADP) receptor. Response to clopidogrel varies widely, with resistance rate ranges 4%–30%. Genetic variations involved in the pharmacology to clopidogrel affect the conversion of produrg to active metabolite (pharmacokinetics affect) or affect on platelet receptors (pharmacodynamics affect). Many studies reported that genetic variations in CYP3A4, CYP2C19 and CYP2C9 affect on prodrug conversion. CYP2C19*2 loss-of-function allele is associated with a marked decrease in platelet responsiveness to clopidogrel. A P2Y1 gene variation, 1622AG, was shown to be associated with a significant effect on platelet ADP response, with a greater response to clopidogrel in carriers of the G allele. Carriers of the P2Y12 H2 polymorphism were reported to affect the platelet response to clopidogrel. The C807T polymorphism affects the Ia subunit of GP Ia/IIa, which is a major platelet collagen receptor, and the expression of the receptor on the platelet surface.

Challenges for Pharmacogenetics

However pharmacogenetics can describe some of variations in drug response among patients, there are challenges in applying it as an analytical tool for individualization of therapy because of the following reasons:

1- Variation in drug response is not affected only by genetic variations.

2- There is a wide controversial in the association of some genes with drug response.

3- Clinical researches are still inadequate to approve the rational use of pharmacogenetics in treatment.

4- Many people may not accept genetic profiling.

5- Distinguishing environmental factors from genetic factors may be difficult.
6- Drug manufacturers may be reluctant to fund research in genetic profiling, and tend to invest in new drugs.
7- Pharmacogenetic targeting may pose ethical problems, which need to be indentified and opened for debate.

Suggested Readings

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