IJPSR (2013), Vol. 4, Issue 8 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 April, 2013; received in revised form, 08 June, 2013; accepted, 15 July, 2013; published, 01 August, 2013

PHARMACOGENOMICS: A STEP TOWARDS PERSONALIZED MEDICINE- A SHORT REVIEW

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Keywords:

Gastric residence time, Floating Drug Delivery System, *In-vitro* evaluation

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ABSTRACT: Pharmacogenetics (PGt) is an established discipline that studies the genetic basis of inter-individual variability in the response to drug therapy and pharmacogenomics (PGx) is the branch of pharmacology which deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity. The goal of personalized medicine is to maximize the likelihood of therapeutic efficacy and to minimize the risk of drug toxicity for an individual patient. Many unexpected pharmacodynamic responses and pharmacokinetic variations among individuals during drug therapy involve genetic factors. These genetic factors contribute to variations at many levels, including drug transport, metabolism, and interaction at the receptor site. Understanding and monitoring the underlying pharmacogenetic factors will allow physicians to optimize efficacy and minimize side effects. In March 2005, the FDA released its final version of the "Guidance for Industry: Pharmacogenomic Data Submissions" clarifying what type of pharmacogenomic data needs to be submitted to the FDA. In addition, the guidance, for the first time, encourages the voluntary submission of data to the FDA. The labeling of many new drugs now contains more information on drug interactions and metabolism based on our understanding of PGt/PGx. With genetic diagnostic tests becoming more common and affordable, it is expected that individual drug dosing will become more accurate and ultimately result in vast improvements in therapeutic response and better drug tolerance.

INTRODUCTION: *Pharmacogenetics* is an established discipline that studies the genetic basis of inter-individual variability in the response to drug therapy and *pharmacogenomics* is the branch of pharmacology which deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(8).2849-52

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.4(8).2849-52

Pharmacogenetics and pharmacogenomics are involved in the study of genes that code for drug metabolizing enzymes, drug receptors, drug transporters and ion channels or efflux systems. Application of pharmacogenetics to pharmaco-kinetics and pharmacodynamics helps the development of models that predict an individual's risk to an adverse drug event and therapeutic response. With some drugs, pharmacogenetics allows the recognition of subgroups with different genetic makeup that result in alterations in drug receptors and the pharmacodynamic response to drugs. By doing so, pharmacogenomics aims to develop rational means to optimize drug therapy, with respect to the patients' genotype, to ensure maximum efficacy with minimal adverse effects.

The outcome of the disease, resistance to treatment and adverse reactions are increasingly recognized as an interaction of the individual's genes and the environment [1]. Such approaches promise the advent of "personalized medicine"; in which drugs and drug combinations are optimized for each individual's unique genetic makeup [2-3].

Pharmacogenomics is the whole genome application of pharmacogenetics, which examines the single gene interactions with drugs. The dream of personalized medicine was one of the driving forces behind the 13 year, $ 3 billion Human Genome Project. Researchers hoped that once the genetic blue print was revealed, they could create DNA tests to gauge individual's risk for conditions like diabetes and cancer, allowing for targeted screening or preemptive intervention.

Genetic information would help doctors select the right drugs to treat disease in a given patient. Pharmacogenetics (PGt), or pharmacogenomics (PGx), a more modern term preferred by some researchers, has been the subject of discussion by industry and regulatory agencies. These groups tried to generate a consensus on how and to what extent should PGx and PGt information be applied to improve drug therapy and safety of both old and new drugs [4].

Although the path or developing new drugs is becoming clear, personalized medicine has an equally important role to play in drugs already on the market. While companies have focused on discovering new pharmacogenomic medicines, academic researchers have begun to apply genomics to the well-understood cytochrome P450 (CYP450) groups of genes, which encode a family of liver enzymes. These enzymes metabolize as many as third of the medicines that are already on the market, from the blood thinner warfarin to codeine to may antidepressants. Recently, Roche Diagnostics received the FDA's approval to market its version of a test for three CYP genes commercially to physicians.

Genetic Polymorphism: Genetic polymorphism is due to the difference in DNA sequence among individuals, groups, or populations. It may be the result of chance processes, or may have been induced by external agents (such as viruses or radiation). If a difference in DNA sequence among individuals has been shown to be associated with disease, it will usually be called a genetic mutation. Genetic polymorphisms or genetic variations can occur with a frequency of greater than 1% of the population, or mutation in less than 1% of the population, can affect patient therapeutic response or metabolism of a given drug [5]. Our understanding of the impact of these genetic differences on clinical pharmacokinetic and pharmacodynamics are in their infancy.

Genetic polymorphism within a specific genotype may occur with different frequencies depending on racial or population factors, which evolved from selective geographic, regional, and ethnic factors. Inter-individual differences in response to drug therapy due to differences in acetylation of drugs are well-studied example of genetic polymorphism.

Patient's ability to metabolize certain drugs such as hydralazine, procainamide and isoniazid can be categorized as either "fast acetylators", "normal acetylators", or "slow acetylators". Acetylators status dependent on the patient's genetic composition, which determine the activity of the acetylation enzyme N-acetyltransferase.

Adverse reactions and Genetic differences: Variations in drug pharmacokinetics and pharmacodynamics are due largely to genetic polymorphism in genes involved in drug metabolism, absorption, disposition, and disease pathogenesis. Many adverse reactions are caused by an inherited deficiency due to genetic variations in enzyme activity. For example, hemolysis is caused by antimalarial drugs is recognized as being caused by inherited variants of glucose-6-phosphate dehydrogenase, slow metabolism of isoniazid in some patients (acetylation of isoniazid) has been found to be the cause of peripheral neuropathy caused by this drug.

There are several known genes which are largely responsible for variances in drug metabolism and response. The most common are the cytochrome P450 (CYP) genes, which encode enzymes that influence the metabolism of more than 80 percent of current prescription drugs. Codeine, Clopidogrel, tamoxifen, and warfarin are examples of medications that follow this metabolic pathway. Patient genotypes are usually categorized into predicted phenotypes.

More recently, a review of the pharmacogenetic literature showed that sizable portions of ADRs (30%) involved in drug therapy implicated genetic polymorphisms of drug metabolism by CYP2D6 [6]. For example, if a person receives one 1 allele each from mother and father to code for the CYP2D6 gene, then that person is considered to have an extensive metabolizer (EM) phenotype. An extensive metabolizer is considered normal. Other CYP metabolism phenotypes include: intermediate, ultra-rapid and poor. Each phenotype is based upon the allelic variation within the individual genotype.

Genetic Polymorphism in Drug Transport:

1. **P-Glycoprotein and Multidrug resistance:** Transport pharmacogenetics is a rapidly developing field that is concerned with drug uptake and efflux into or through tissues. Significant problems in the clinical application of drugs result from poor or variable oral drug bioavailability and high intra and inter-individual variations in pharmacokinetics. Several membrane transporter proteins are involved in the absorption of drugs from the intestinal tract into the body, into non-intestinal tissues, or into specific target sites of action [7].

   Drug efflux is an important cause of drug resistance in certain types of cells. In cytotoxic chemotherapy for several human cancerous diseases, drugs are generally effective, but in case of intrinsic or acquired multidrug resistance, many highly effective antineoplastic drugs like vincristine, vinblastine and doxorubicin fail to produce cures. P-glycoprotein multidrug transporter, or MDRI, which is one of the major causes of low drug level in targeted cells [8]. The multidrug-associated proteins (MRPs) are members of the ATP-binding cassette (ABC) superfamily with six members currently, of which MRP1, MRP2, MRP3 are commonly known to affect drug disposition.MRP1 is present in abundance in the body and substrates include glutathione, glucuronide, and sulfate.

2. **Genetic polymorphism in Drug Targets:** In the future, proteins involved in disease will become identified as important biomarkers for pharmacodynamic studies. Genomics has led to the development of proteonomics, which involves the study of biologically interesting proteins and their variants. Proteins can be used as probes for drug discovery or as biomarkers for drug safety, such as cell surface proteins (e.g., COX-2, D-2R), intracellular proteins (e.g., troponin 1) and secreted proteins (e.g., MCP-1).

APPLICATIONS: Seven years ago, the approval of the breast cancer drug Herceptin (Genetech, CA) created a stir both in the medical community and the popular press. It helped only about one in five women who took it. But those women turned out to have a mutation in their tumor cells that clearly differentiated them from non-responders. In March, however, the FDA produced a long-awaited guidance document clearly specifying what kinds of genomic data it will require for drug approvals, and encouraging companies to submit preliminary data voluntarily in order to help build a scientific basis for interpreting pharmacogenomic experiments.

The agency is now working with companies to develop another set of guidelines to define the process for validating biomarkers. But regulatory issues aside, the pharmaceutical industry has also had a strong profit motive in avoiding personalizing medicine. Part of their reluctance has come from the desire to not limit their market--a test identifying who will (and who won't) respond to a drug means that fewer patients will buy it.

Although, many studies have shown the relationship between CYP450 genes and specific drugs, very few have actually correlated the relationship with dosing guidelines that physicians can use. But conducting the prospective studies to establish that dosing is gene-dependent "takes a lot of effort, a lot of time and a lot of money". Pharmacogenomics has applications in illnesses like cancer, cardio vascular disorders, depression, bipolar disorder, attention deficit disorders, HIV, tuberculosis, asthma, and diabetes.

In cancer treatment, pharmacogenomics tests are used to identify which patients are most likely to respond to certain cancer drugs. In behavioral health, pharmacogenomic tests provide tools for physicians and care givers to better manage medication selection and side effect amelioration. Pharmacogenomics is also known as companion diagnostics, meaning tests being bundled with

drugs. Examples include KRAS test with cetuximab and EGFR test with gefitinib. In cardiovascular disorders, the main concern is response to drugs including warfarin, clopidogrel, beta blockers, and statins. Many people take medications called SSRIs, or selective serotonin reuptake inhibitors, for different psychiatric disorders. Many of the medications are metabolized by CYP450 enzymes, including fluoxetine, paroxetine, and citalopram.

Gene SightRx, a test provided by AssureRx Health, is an example of a product that provides information to health care providers about an individual patient's genetic variability in response to multiple antidepressant and antipsychotic medications. Health care providers can use this information to help determine which medications maximize benefits while minimizing side effects.

Personalized medicine focuses on individualized drug treatment according to each patient's molecular diagnosis and genetic makeup. Individualized drug therapy involves optimal drug selection and rational dosage adjustment. Although not all drugs can be personalized, there is most likely to be clinical significance in tailored medicine for prodrugs, drugs with narrow therapeutic drugs and drugs that target a key molecule or a critical pathway. Drug safety is the first arena in which patients can benefit from pharmacogenetics and pharmacogenomics. Tumor responses to the inhibitors of oncogenic tyrosine kinases are associated with the presence of activating mutations within the genes encoding the target kinases; targeted cancer therapy is thus a promising individualized drug therapy.

In March 2005, the FDA released its final version of the "Guidance for Industry: Pharmacogenomic Data Submissions" clarifying what type of pharmacogenomic data needs to be submitted to the FDA and when. In addition, the guidance, for the first time, encourages the voluntary submission of data to the FDA. These so called voluntary submissions of data to the FDA are providing a novel platform for a scientific exchange of data that is outside of the normal regulatory review process and can be used to share exploratory and research data that is not used for regulatory decision making.

CONCLUSION: The successful application of genetic screening tests to identify patients with specific risks in drug response or drug toxicity depends on many factors. Large amounts of relevant genetic information must be monitored. Robust, high throughput, high positive and low negative predictive tests must be developed and implemented. Such an endeavor will also involve considerable training, adaptation and acceptance of the new technology by physicians and other health care personnel.

With genetic diagnostic tests becoming more common and affordable, it is expected that individual drug dosing will become more accurate and ultimately result in vast improvements in therapeutic response and better drug tolerance. Researchers have high expectations that the use of diagnostic DNA microarrays or gene chips will simplify and expand testing and have clinical applications in diagnosis, disease prevention, drug selection and dose calculation.

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How to cite this article:
Jacob S, Anoop S and Thomas T: Pharmacogenomics: A step towards Personalized Medicine- A Short Review. *Int J Pharm Sci Res* 2013: 4(8); 2849-2852. doi: 10.13040/IJPSR. 0975-8232.4(8).2849-52