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Pharmacogenetics: Are We Ready For the Era of Personalized Medicine?

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Editorial

The story which is commonly happened in the hospitals every day is the variability of drug response among patients which ranged between failure of treatment to adverse drug reactions and toxicities and may be death. For examples, ACE inhibitors (angiotensin converting enzyme inhibitors) that improve symptoms and survival in cases of congestive heart failure (CHF) and also in treatment of hypertension, the % of non-respondents ranged between 10 and 30% while in case of other drugs like B-2 agonists used in treatment of asthma are ranged between 40-70%.

One major reason underlying insufficient response or problems of tolerability or toxicity is the considerable interindividual variability in the pharmacokinetic properties of the patients. Patients differ in their ability to absorb, distribute, metabolize and excrete drugs due to concurrent disease, age, concomitant medication or genetic peculiarities. At the exact same dose, a more than 20-fold interindividual variation in steady state concentrations of the drugs in the body may result.

The discoveries of novel genetic polymorphisms in drug transporters, and metabolizing enzymes have given an insight into the biological phenomena of drug efficacy and toxicity. For example, it was also found that the inter-individual variations in the human genome may affect both, risk of type 2 diabetes mellitus (T2DM) development and personalized response to identical drug therapies. Clinically, it is observed that T2DM patients who receive identical oral antidiabetic agents (OADs) often exhibit significant variation in glycemic control, glycated haemoglobin (HbA1c) level, drug efficacy, tolerability and incidence of adverse effects.

The question now is “how can physicians prescribe drugs that will be effective for everyone and without adverse drug effects?” This may be done via the application of pharmacogenetic testing. Pharmacogenetic approaches focus on testing single nucleotide polymorphisms (SNPs) and their influence on the individual drug response, efficacy and toxicity. If the physicians know from the beginning how each person's body handled different drugs, they could prescribe the right dose of the right drug rather than having to guess as they do today.

In the future a patients' genetic profile may be available in their medical records; giving physicians a glance guide to which drugs will be effective for that person. Pharmacogenetics establishes the use of an individual’s genetic information to guide treatment therapy and has become an important tool in achieving “personalized medicine”.

Research studies revealed that between 20 and 25% of all drugs in clinical use are metabolized at least in part by

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CYP2D6. Subjects with multiple gene copies will metabolize drugs more rapidly and therapeutic plasma levels will not be achieved at ordinary drug dosages. Individuals lacking functional CYP2D6 genes metabolize selective CYP2D6 substrates at a lower rate, and consequently at higher risk for adverse drug reactions. The CYP2D6 genotype has been successfully shown to predict the clearance of the antidepressants desipramine, fluvoxamine, mexiletine, mianserin, nortryptiline, and paroxetine as well as the clearance of the neuroleptics perphenazine and zuclopenthixol and the competitive muscarinic receptor antagonist tolterodine. Adverse effects due to elevated drug plasma levels occur more frequently in poor metabilzers (PMs) in cases where the drug clearance is dependent on CYP2D6. A lack of CYP2D6 enzyme results in reduced effectiveness of drug therapy in instances where prodrugs requiring activation by CYP2D6 are used. This is seen for the analgesic effect of tramadol and codeine.

Other example is the use of sulfonylureas (SUs) as insulin secretagogues OADs. This group of drugs is considered as one of the most common classes of OADs being prescribed either alone or in combination since 1960s. Sulfonylureas like tolbutamide, glimperide, glipizide and glibenclamide are metabolized to active metabolites in the liver mainly by cytochrome P450 2C9 (CYP2C9) and then excreted by the kidney. It has been reported that CYP2C9 gene variants were significantly associated with efficacy of SUs in diabetic patients. Two variants of CYP2C9 gene, CYP2C9*3 and CYP2C9*2 have been significantly associated with missense mutations and amino acid polymorphisms resulting in decreased metabolism of SUs in healthy individuals. For this reason T2DM patients treated with SUs and with CYP2C9*3 variant were found with an enhanced risk of severe hypoglycemia. Consequently, those T2DM patients with CYP2C9 gene variants were reported for 30%-80% reduction in renal clearance of glibenclamide suggesting lower doses of this antidiabetic drug to decrease the risk of hypoglycemia

The technology to identify SNPs is available, and databases that house these SNPs and gene sequence information are rapidly growing and readily accessible. The Roche AmpliChip CYP450 test is used nowadays to identify a patient's CYP2D6 and CYP2C19 genotype from genomic DNA extracted from a whole blood sample of the patient. Information about CYP2D6 and CYP2C19 genotype may be used as an aid to clinicians in determining therapeutic strategy and treatment dose for therapeutics that are metabolized by CYP2D6 or CYP2C19 gene product.

In conclusion, pharmacogenetics will play an important role in predicting a patient's drug activation and detoxification status, such that a therapeutic intervention can be made prior to drug administration without exposing the patient to drug toxicity or therapeutic failure. Pharmacogenetics will continue to play a key role in defining strategies to optimize drug therapy and individualized medicine.