Pharmacogenomic studies: hype & reality

Though pharmacogenomics is the latest buzz word in medical research. It is important to note that the subject is not very young. History of pharmacogenetics could be traced to the first inherited difference in a response to a chemical, i.e., inability to taste phenythiourea in 1932. This was followed by reports of haemolysis in African-American soldiers treated with primaquine highlighting importance of genetic deficiency of glucose-6-phosphate dehydrogenase (G6PD). Shortly following this Motulsky suggested that inheritance might explain many individual differences in the efficacy of drugs and in the occurrence of adverse drug reactions. In 1959 Vogel coined the term “pharmacogenetics”. In 1960, a study showing genetic polymorphism influencing blood concentrations of isoniazid was also published. What has changed perhaps over the years is the expectations with pharmacogenomics. Pharmacogenomics is increasingly being recognized as an independent discipline. It was believed that the era of using personalized medicine devoted by the individual’s genotype had began. However, it was soon realized that pharmacogenetics may not be as useful for personalized medications as was initially perceived.

A polymorphism is a variation in the DNA sequence that is present at an allele frequency of 1 per cent or greater in a population. Two major types of sequence variation have been associated with variation in human phenotype - single nucleotide polymorphism (SNPs) and insertions/deletions (indels), the latter being relatively infrequent.

The pharmacogenetic information exhibits a kind of hierarchy with only a fraction of SNPs leading to a clinically significant effect. Of the approximately 20-80 million known SNPs, only about 300,000 represent exon based change. Non-synonymous SNPs which result in change in the amino acid, are still fewer with chances of phenotypic changes being higher if these SNPs result in the non conservative amino acid changes. Of the ones showing changes in the conservative region, only a smaller fraction leads to a change in activity in vitro and further less in pharmacokinetic parameters or drug response which leads to a change in clinical outcome.

Cytochrome P450 enzymes have been extensively evaluated for pharmacogenetic variability. After the first identification of genetic changes responsible for altered activity in the metabolism of CYP2D6 substrates, the number of such identified genetic changes has grown exponentially and can be accessed from http://www.imm.ki.se/CYPAlleles. There is a great deal of geographic variation in the frequencies within human populations. For instance, the incidence of poor metabolizer phenotype for CYP2D6 varies considerably in different human populations, from an average of 7 per cent in Caucasians to about 2 per cent in the African or Asian populations. In view of this knowledge generating indigenous data is of utmost importance.

In this issue, Rosemary et al., have evaluated the implications of SNP of CYP2C9 and CYP2C19 genes on phenytoin pharmacokinetics. They have evaluated the influence of CYP2C9 and CYP2C19 polymorphism...
on phenytoin hydroxylation in healthy south Indian subjects. Since these enzymes are involved in the metabolism of phenytoin, one of the widely used antiepileptic drug with a narrow therapeutic index, such a study gives some important information. The authors have shown that the *2 - *3 alleles of CYP2C9 led to decreased hydroxylation of phenytoin in vivo, whereas the mutant alleles of CYP2C19 played only a minor role in the metabolism of phenytoin. An earlier report by the same authors have shown that the frequency of CYP2C9 *2 mutant allele in south Indians was higher than in Chinese and Caucasians, while the frequency of the *3 allele was similar to Caucasians. They had also identified high frequency of CYP2C19*2 allele in this population.

Earlier studies have demonstrated that both *2 and *3 alleles of CYP2C9 can affect phenytoin pharmacokinetic. *2 carriers were shown to have increased serum concentrations of phenytoin after a single dose in healthy volunteers. This was attributed to decreased clearance. Similar reduction in phenytoin clearance has been noted with *3 allele of CYP2C9. In another study, a significant association of maximum dose of drug with CYP2C9 * 3 allele has been shown. It was hypothesized in the study that the genetic analysis may make it possible to safely deduce the time required to deduce an effective dose. Attempts have also been made to recommend a dose range for a particular genotype.

The functional relevance of studying any pharmacogenic variation is of utmost importance. With the use of probes, the phenotypic variations resulting from the various genotypes have been evaluated. While identification of genetic variation could be beneficial for research purposes, for using such information in clinical practice, chemical probes which easily identify outliers, might make more economic sense.

Of the various genetic variations affecting pharmacokinetics of a drug, perhaps the most clinically significant polymorphism is the thiopurine methyltransferase (TPMT) polymorphism. TPMT is involved in the methylation of thiopurines such as mercaptopurine. One in 300 individuals is a homozygous deficient, 10 per cent are heterozygots, and about 90 per cent are homozygous for the wild TPMT allele. Methylation of mercaptopurine competes with activation of the drug to thioguanine nucleotides, the concentration of the active thioguanine metabolite (which is also responsible for its toxic potential) is inversely related to TPMT activity and directly related to the probability of pharmacologic effects. For homozygous deficient patients who can tolerate less than 10 per cent of the dose tolerated by the homozygous wild type patients, a dose reduction may be required to avoid myelosupression. Since mercaptopurine is a drug with a narrow therapeutic index, dosing by trial and error can lead to fatal consequences and genotyping may be useful in adjustment of thiopurine doses. These variants also have clinically important intolerance to azathioprine. In evaluating TPMT pharmacogenetics a ‘phenotype to genotype’ approach was adopted. This was achieved by detecting outliers in clinical population relatively early and working backgrounds. This approach is increasingly being recognized as the more practical approach because functional importance of the variant is known in advance.

Though the effect of genomic variations has been more commonly evaluated on the pharmacokinetic aspects of drugs, there are several examples in which genetic variations leading to altered pharmacodynamic response have been evaluated. Notable among these is the use of tamoxifen in patients with (ER) positive breast carcinoma cells. The methylene tetrahydrofolate reductase (MTHFR) polymorphism has been linked to homocysteinaemia, which in turn affects thrombosis risk. B-adrenoreceptor mutations have similarly been noted to demonstrate altered response to drugs. A677T > C mutation in the MTHFR gene may lead to a lower activity of MTHFR and may predispose to gastrointestinal toxicity to methotrexate in stem cell transplant recipients. Polymorphism in the genes for ion channels such as HERG, KvLQT1 may predispose to drug induced arrhythmia. It is time now that the studies on
pharmacogenetics be guided more by considering clinical utility than anything else.

A wider application of this field would be to evaluate its role in drug development. Using microarray technology, one could identify genes whose expression differentiates inflammatory processes, a compound could be identified that changes expression of the gene and then that compound could serve as a starting point for anti-inflammatory drug development. The pharmacogenetics knowledge may be beneficial in selection of patients in clinical trials. Selection of patients who are more likely to respond and less likely to develop adverse event may improve success rate of some potentially useful new chemical entities. Even FDA has come up with a guidance document on pharmacogenetic studies in drug development process. It is very likely to become a regulatory requirement soon.

In conclusion, the field of pharmacogenetics has grown from an occasional publication to a distinct entity. A recent PubMed search with pharmacogenomics got 3600 hits. Judicious application of the knowledge obtained from these studies would make the findings clinically meaningful.

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References


