Letters to Editor
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Polymorphism of Drug Metabolism: Does It Matter?

Sir,

Genetic diversity influences various traits in the human race such as hair color, eye color, and skin color, and this diversity is of no exception to the way individuals' metabolize drugs. The metabolism of drugs is in part genetically controlled causing variations in drug metabolism among individuals. The liver is the principal site for drug metabolism. Other sites include the kidneys, gastrointestinal tract, skin, and lungs.[1] This letter explains polymorphism of drug metabolism with regards to genotype and phenotype. It further addresses the significance of polymorphism of drug metabolism.

With particular concern to the liver, genetic variations in drug metabolism is influenced by differences in the genetic coding for drug metabolizing enzymes. Consequently, a proportion of the population will manifest a drug metabolizing enzyme which is different in structure and function from the rest of the population. This variation is termed polymorphism of drug metabolism when such genetic variant occurs in, at least, 1% or more of a given population. This is contrary to mutation in which the genetic variation occurs in <1% of the population and results in an allele of a rare or abnormal nature from the wild-type.

Genetic polymorphism occurs as a result of "gross structural changes including complete gene deletion, gene duplication, and genetic translocation" or single-nucleotide polymorphism (SNP) occurring at one specific point in the nucleotide sequence of the gene.[2] This consequently causes a change in the normal nucleotide sequence resulting in a variant allele compared with the wild-type. For drug metabolizing enzymes such as any other enzyme, the position of each amino acid in the sequence coded by the gene is critical to its function. Hence, any variation in the genetic coding for these enzymes as a result of polymorphism will ultimately influence the enzyme activity. Complete gene deletion leads to lack of enzyme formation and consequently enzyme activity since there will be no coding for the amino acid sequence for the particular enzyme. Genetic translocation, on the other hand, will yield a nonfunctional product which leads to no activity. Genetic duplication and multiplication will also cause over expression of the enzyme activity except for duplication involving a variant form of allele which causes loss of activity.

The effect of polymorphs on enzyme product arising from SNP is dependent on the location; the polymorphism occurs on the gene structure. Gene regulation is affected when SNP occurs at the 5' domain which is responsible for transcription control of gene expression. SNP occurring at the intron portion of the premessenger RNA (mRNA) of the gene has normally no influence on the mature mRNA unless the SNP occurs at any of the nucleotide (e.g., adenosine or guanine) involved in the slicing of the pre-mRNA to mature mRNA. The later results in either loss or decrease in the function of the enzyme product formed. However, SNP occurring at the exon portion which is directed amino acid sequence for enzyme formation and other protein products may cause one or more of three possible consequences of nucleotide substitution. The possible consequences are the same codon, a different codon, or a stop codon formed for the intended amino acid sequence.[3]

As mentioned earlier, drug metabolizing enzymes are not an exception from the above-mentioned forms of genetic polymorphs, and these polymorphs predominantly influence Phase 1 and Phase 2 of drug metabolism in the principal organ; the liver. During Phase 1 drug metabolism, the effect of genetic polymorphism

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influences drug metabolizing alleles. These drug metabolizing alleles are located on each chromosome of the pair of inherited somatic chromosomes. For homologous individuals, the same drug metabolizing allele (two copies of either dominant or recessive) is inherited from both parents. Heterozygous individuals do inherit different allelic form of the gene from each parent consisting of one dominant and one recessive gene. In some cases, double heterozygous occur which indicate the individual is heterozygous for more than one variant of the allele.[2] The physical expression of these inherited alleles gives rise to what is known as phenotyping.

The phenotype is deduced by measuring the metabolic ratio of a test drug which is metabolized solely by specific drug metabolizing enzyme. The metabolic ratio is as the ratio of the administered dose of the test drug to the measured serum or urine metabolite.[4] Once the phenotype of the test drug is determined in an individual, the phenotype of other substrates metabolized by the same drug metabolizing enzyme can be predicted. The expression of the phenotype may either be "toxic plasma concentrations" or "lack of pharmacological response."[5] The toxic plasma concentration is expressed by the phenotype classified as "Poor Metabolizers (PMs)" which occur as a result of autosomal recessive traits. Conversely, the phenotype responsible for lack of pharmacological response is characterized as "Extensive Metabolizers (EMs) or ultra-extensive metabolizer" resulting from autosomal dominant trait giving rise to rapid elimination of the metabolized drug.[5]

Knowledge about polymorphism in drug metabolism is therefore highly significant. Genotyping helps in predicting the therapeutic response of other drug substrates from a known therapeutic response to a particular drug metabolizing polymorph. CYP450 enzymes have caused an enormous positive leap in clinical practice. An example is the isoenzyme CYP 2D6 which has been extensively characterized for its genetic polymorphs. This isoenzyme gained recognition following adverse effects from a subgroup of clinical trial population administered debrisoquine or oxytocic sparteine. Mutations giving rise to both increased and decreased metabolism have been identified and classified individuals into EM or PM, respectively. Debrisoquine and oxytocic sparteine have also served as test drug to predict the phenotypes of other drug substrates for CYP 2D6 which include antipsychotics, antidepressants, and beta blockers, which will ultimately predict the therapeutic response or adverse reactions of these drugs.

Furthermore, understanding of polymorphism enables effective drug efficacy assessment. This helps in understanding the different efficacy outcomes of the same medicine in different patient population to help in personalized treatment schedules. A typical example is sulfasalazine efficacy assessment in the treatment of chronic discoid lupus erythematosus.[4] In the assessment, a percentage of the patient population showed marked improvement whereas others did not. A genotype investigation into these unpredictable and different outcomes concluded on the influence of the polymorphic nature of the acetylating enzyme N-acetyltransferase 2 (NAT 2) on the acetylation of sulfasalazine. Those who showed marked improvement were identified as rapid acetylators on the contrary to slow acetylators who showed no response to sulfasalazine. This led to genotyping patients prior to administration of sulfasalazine in order to ascertain its efficacy.

In addition, knowledge of polymorphism is also relevant in pharmacovigilance to monitor the safety and adverse reactions of medicines. Following on NAT2, adverse reactions in HIV/AIDS patients to sulfonamides have been linked with these patients being identified as slow acetylators.[5] In addition, medicines with narrow therapeutic range are being prescribed safely, based on genotype information so that the therapeutic effect/toxic ratio could be balanced effectively to derive maximum effect and minimize toxic response in patients. A good example is warfarin, which has achieved safe prescription through dose adjustments based on genotypying despite its narrow therapeutic index.

Another significant impact of polymorphism in drug metabolism is in the area of drug discovery and development. For example, the PRESTO trial was terminated as a result of lack of efficacy of tranilastin the management of restenosis. In addition, the trial observed the hyperbilirubinemia in 4% of trial patients as a result of polymorphic urine diphosphate glucuronosyltransferase 1A1 gene identified as Gilbert's syndrome.[5] Although the termination was not due to the adverse effect, 4% (more than 1%) occurrence in the population makes this variation a significant polymorph which would have influenced prescribing protocol to be based on genotyping, if it had been approved for the management of restenosis.

2. Conclusion

Polymorphism in drug metabolism hugely influences the discovery, development, safety, efficacy, and prescribing pattern of medicines. Genotyping predominantly predicts the phenotype of drug metabolizing enzyme in an individual. Nonetheless, the phenotype is not always predictive of the genotype due to other confounding environmental factors such as concomitant administration or a disease state. A typical example is a competitive inhibition CYP 2D6 enzyme by selective serotonin reuptake inhibitor (e.g., fluoxetine). Hence, the concomitant administration may cause an EM to be expressed as PM depending on the concentrations. Therefore, polymorphism of drug metabolism should be approached holistically always having an open mind for unexpected occurrences.

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3. Source of Support

Nil.

4. Conflicts of Interest

None declared.

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