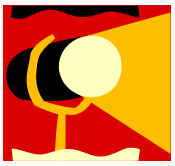
GENOMIND®

Spotlight on Phenoconversion



There are six Cytochrome P450 (CYP450) genes tested in the Genecept Assay® and utilized by G-DIG (the Genomind Drug Interaction Guide)®. Based on variation within these genes, there are four potential phenotypes, which may impact drug efficacy and adverse events: Poor Metabolizer (PM), Intermediate Metabolizer (IM), Extensive/Normal Metabolizer (EM) and Ultrarapid Metabolizer (UM). However, it is important to go beyond consideration solely of genetic influences on drug metabolism and also take into account drug effects on metabolizer status.[1,2]

The term phenoconversion has been used to describe the potential for specific drugs to inhibit or induce CYP enzymes, thereby altering genetically based metabolism status.[1] Various studies use therapeutic drug monitoring to assess the metabolic ratio, which compares the concentration of the metabolite to that of the parent drug, and is thus reflective of the true clinical phenotype. This clinical phenotype is then compared to the phenotype associated with genetic variation in order to assess the occurrence of phenoconversion.

Using this method, individuals who are genetically EM, IM, or UM may exhibit a clinical phenotype of PM when exposed to certain drugs or environmental factors. Studies of risperidone metabolism have demonstrated that paroxetine, fluoxetine, and other CYP2D6 inhibitors may cause phenoconversion in 50% of genetic EMs, and 83% of genetic IMs.[3,4] Additionally, a study by Preskorn and colleagues examined metabolism of the SNRI venlafaxine to assess the prevalence of CYP2D6 phenoconversion in patients taking concomitant medications. Only 4% of individuals in the study were genetically defined PMs, but 27% of participants were clinically PMs, suggesting considerable phenoconversion. Further analysis showed that phenoconversion was more frequent in individuals who were taking other CYP2D6 substrates and inhibitors (40%) than in those not taking other CYP2D6 substrates and inhibitors (13%, $p<0.0001$).[5]

As demonstrated by these studies and reviewed in our previous Spotlight on inhibitors and inducers, various antidepressants and other psychiatric drugs may act as inhibitors and inducers of the CYP450 enzymes.[6] In addition, common over-the-counter medications and herbal remedies can contribute to phenoconversion. Environmental factors are also important to assess, especially for CYP1A2 substrates like clozapine, for which factors like smoking may induce enzyme activity and phenoconvert individuals to UM status.[2]

Therefore, it is important to possess the knowledge and tools to consider these pharmacological and environmental factors and their effects on CYP450 phenotypes. G-DIG (The Genomind Drug Interaction Guide)® was developed to assist in evaluating the interaction between a patient's genetics, co-administered drugs, and certain environmental factors on the CYP450 enzymes. This tool is available to all Genecept ordering clinicians and provides a personalized drug-gene-environment interaction profile for each patient tested by Genecept.

References

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4. de Leon J, Sandson NB, Cozza KL. A preliminary attempt to personalize risperidone dosing using drug–drug interactions and genetics: part II. Psychosomatics 2008; 49: 347–61.
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6. E Tanaka, S.H., *Clinically significant pharmacokinetic drug interactions with psychoactive drugs: antidepressants and antipsychotics and the cytochrome P450 system.* Journal of Clinical Pharmacy and Therapeutics, 1999. **24**: p. 7-16.