Xenobiotic Metabolizing Enzymes and Xenobiotic Receptors. Pharmacological and Toxicological Aspects, 2010: ISBN: 978-81-7895-437-0 Editor: Guillermo Elizondo Azuela

1. CYP2D6 polymorphism and its clinical implications

Martha Sosa Macias and Ismael Lares Asseff

Centro Interdisciplinario de Investigación para el Desarrollo Integral Regional del Instituto Politécnico Nacional- Unidad Durango (CIIDIR-IPN), México

Abstract. CYP2D6 is the most important enzyme in the metabolism of drugs and is responsible for the metabolism of 25% of all drugs currently available on the market. CYP2D6 is not only expressed in liver but also in gut and brain neurons, where endogenous substrates with high turnover have been found. Expression of CYP2D6 is not regulated by any known environmental agents and is not inducible by known hormones, in contrast to other hepatic xenobiotic metabolizing cytochrome P450s. CYP2D6 activity is inherited as a monogenetic trait, and the *CYP2D6* gene appears to be highly polymorphic in humans. The polymorphic alleles may lead to altered activity of the CYP2D6 enzyme causing absent, decreased, or increased metabolism that in turn influences the disposition of about 50% of metabolized drugs. Currently, more than 63 different functional CYP2D6 gene variants have been described. Among them, the most important variants are *CYP2D6*4* (splice defect) and *CYP2D6*5* (gene deletion), whereas the common alleles with severely reduced activity are *CYP2D6*10*, *CYP2D6*17*, and *CYP2D6*41* (splicing defect). *CYP2D6*17* decreases CYP2D6 activity in a substrate-dependent fashion, however this has not been shown for other variants. The *CYP2D6* gene is subject to many copy number variants. These gene duplication events include functional, partly functional, and nonfunctional genes. Duplication or multiplications of active *CYP2D6* genes results in ultra-rapid enzyme activity. The *CYP2D6* alleles are subject to very important interethnic differences. The poor metabolizer phenotype (PM) is mainly found in Europe and the ultrarapid metabolizer phenotype (UM) in North Africa and Oceania, whereas the intermediate metabolizer phenotype is mostly located in Asia, due to the high prevalence of the *CYP2D6*10* allele. Therefore, for clinical trials and drug therapy, the allelic constitution of a given patient is an important aspect to consider with respect to proper dosing and registering a genotype-phenotype. In the past, the PM phenotype has been much discussed in relation to adverse reactions. However, the UM phenotype has also been associated with adverse drug reactions, mainly as a result of high levels of drug metabolites. The CYP2D6 polymorphism appears to be the most clinically relevant of all presently known polymorphic genes with respect to drug therapy.