INVITED LECTURES – ABSTRACTS
VABLJENA PREDAVANJA – POVZETKI

PHENOTYPE-GENOTYPE RELATIONSHIPS OF DRUG-METABOLIZING ENZYMES IN HUMAN LIVER

Mike Ufer
Institute of Pharmacology, University Hospital Schleswig-Holstein, Kiel, Germany;
mufer@pharmakologie.uni-kiel.de

Most drugs are eliminated from the body by hepatic biotransformation that is catalyzed by Phase I and II metabolizing enzymes. The expression levels and catalytic activity of these enzymes is predictive for the drug clearance and hence for the plasma concentration obtained following intake of a certain dose. Phase I metabolic reactions are primarily oxidative processes catalyzed by cytochrome P450 (CYP) enzymes, while Phase II metabolism refers to the conjugation of the parent compound or more commonly its Phase I metabolite with glucuronic acid, glutathione or sulphate mediated by various transferase enzymes. There are two principal methods to predict the activity of drug-metabolizing enzymes in human liver termed phenotyping and genotyping.

Phenotyping is usually done by oral administration of a certain probe drug that is selectively metabolised by the enzyme under study. Subsequently, the plasma or urine concentration of probe drug and generated metabolite is measured and the so-called metabolic ratio of drug vs. metabolite is calculated. This ratio is inversely correlated with the current real-time enzyme activity and allows for the assignment of different phenotypes termed ultrarapid (UM), extensive (EM), intermediate (IM) and poor metabolizer (PM). More recently, a number of different cocktail approaches for CYP phenotyping have been proposed dealing with the simultaneous administration of multiple, CYP-specific probe drugs. An alternative approach comprises the intravenous administration of a radioactively-labelled probe drug with subsequent quantification of $^{14}CO_2$ in exhaled air. However, this approach has so far only been established for CYP3A4 phenotyping as so-called erythromycin breath test.

Genotyping of drug-metabolizing enzymes has been greatly facilitated in recent years by the implementation of high-throughput technologies (e.g. real-time PCR, pyrosequencing, MALDI-TOF mass-spectrometry etc.). Completely inactive P450 alleles have been reported for CYP2D6, 2C19, 2A6 and 3A5 due to a lack of enzyme expression or expression of an inactive enzyme thereby leading to a PM phenotype. In addition, the CYP2D6 and CYP2C19 UM phenotype may be adequately predicted by the number of active alleles determined in the course of genotyping. However, the clinical usefulness of CYP genotyping is often hampered by a poor genotype-phenotype correlation of enzyme activity with respect to the most common EM and IM phenotypes. This can be the consequence of drug-drug interactions that may transform a patient with a normal or so-called wild-type genotype and hence with an anticipated EM phenotype to a UM or PM upon exposure to inducers or inhibitors of CYP enzymes, respectively. Another reason for a poor genotype-phenotype correlation stems from the differential reduction of enzyme activity depending on the substrate metabolised among subjects with heterozygous expression of a defective allele.

In summary, most genetic polymorphisms leading to an altered expression and activity of drug-metabolizing enzymes appear to be known and in many instances allow for a prediction of the corresponding phenotype. Such information is presently considered in the course of drug development and candidate drugs selectively metabolised by polymorphic enzymes are often dropped in early drug screening. Despite an eventually limited genotype-phenotype correlation of enzyme activity, it would certainly be advisable to conduct a genotyping analysis once in a lifetime and include such information in the patient's medical record to improve drug safety and efficacy.