

Abstract

Frequency of selected genetic polymorphisms of cytochrome P450 in the Czech population and the influence of CYP2C9 genotype on the hypolipidemic effect of fluvastatin

Introduction: One of the main factors of genetically determined variability in response of humans to administered drugs are differences in catalytic activity of metabolizing enzymes, which are caused mainly by genetic polymorphisms in cytochrom P450 family enzymes. This thesis consists of two parts and it is presented as a commentary to the original papers. The first aim was to investigate the frequency of functionally important variant alleles of three main isoenzymes of cytochrome P450 gene: CYP2D6, CYP2C9, CYP2C19, throughout the Czech population, predict the prevalence of poor metabolizer phenotypes, and then to compare the results to the data from other populations. Secondly, we analysed the correlation between the CYP2C9 genotype and cholesterol-lowering effect of fluvastatin in human hypercholesterolemic patients.

Methods: Genotypes were determined by PCR–RFLP. The presence of alleles CYP2D6*1, *6, *5, *4, *3, and gene duplication was analysed in 233 healthy volunteers, CYP2C9*1, *2 and*3 in 254 subjects and CYP2C19*1, *2 and *2 in 218 subjects. Eighty seven patients on fluvastatin therapy, and 48 patients on monotherapy were enrolled in the prospective fluvastatin study without any interventions to standard procedures of hypolipidemic treatment. Biochemical and clinical data were collected before the initiation of fluvastatin treatment (80 mg/day) and 12 weeks later.

Results and conclusions: There are 6.7% of CYP2D6 poor metabolizers and about 2% of CYP2C19 and CYP2C9 poor metabolizers in the Czech population. The frequencies of the most important functional variant alleles of CYP2D6, CYP2C9 and CYP2C19 and their predicted phenotypes in the Czech population are in concordance with other Caucasian populations. The hypolipidemic effect of fluvastatin was found to be partly influenced by CYP2C9 genotype. Subjects with the CYP2C9*1/*3 genotype achieved a greater reduction in plasma levels of LDL-cholesterol than subjects with CYP2C9*1/*1 or *1/*2 genotypes (39.95% vs. 22.35% or 29.92% respectively), and similar trend was observed in reduction of total cholesterol levels. However, due to rare occurrence of the *3/*3 genotype it was impossible to report a definitive genotype-effect association.

In conclusion, by implementing the genotyping methods and by detemining the frequency of occurrence of the main genetic polymorphisms in CYP isoenzymes, which were reported to account for the metabolism of 40% of administered drugs, we have laid basis for future research into the clinical applications and the development of individualized pharmacotherapy.

Keywords: cytochrome P450, CYP2D6, CYP2C9, CYP2C19, single nucleotide polymorphism, pharmacogenetics, Czech population, individualized pharmacotherapy, fluvastatin, hypercholesterolemia