Abstract

Frequency of occurrence of selected single nucleotide polymorphisms of CYP2C8 and MDR1 in the Czech population and their influence on the effect of amiodarone

Introduction: Variability in drug response is sometimes conditioned by genetic differences in the metabolism and the transport of drugs. Interindividual differences are often caused by polymorphisms affecting biotransformation activity of enzymes and expression of transporters. In the thesis we paid attention to the cytochrome P450 CYP2C8 and MDR1. First, we described the frequency of occurrence of selected variant alleles CYP2C8 * 2, CYP2C8 * 3 (2 substitution in exon 3 and 8, CYP2C8 and CYP2C8 * 3G416A * 3A1196G), CYP2C8 * 4, CYP2C8 P404A in the healthy Czech population and MDR1 variant alleles in these exons: 26 C3435T, 21 G2677A/T, 12 C1236T a 17 T-76A. Subsequently, we studied the influence of these polymorphisms on effects of amiodarone in the selected group of patients.

Methods: We determined genotypes MDR1 a CYP2C8 by PCR-RFLP by using restriction enzymes and specific primers. We determined the frequency of MDR1 genotypes in 189 healthy volunteers and CYP2C8 in 161 healthy subjects. Further we included into the study 63 patients treated with amiodarone for longer than two months. Their treatment was assessed from medical records and by using standard biochemical and haematological examinations and ECG. Concentrations of amiodarone and its metabolite N-desethylamiodarone were evaluated by HPLC analysis.

Results and conclusions: Reduced expression of the MDR1 gene, which is associated with the occurrence of the variant 3435T allele in exon 26 in homozygotes, was found in 33.9% of subjects. The most frequent variant allele CYP2C8*3 associated with lower phenotype activity of the enzyme was found in 10.9% of the Czech population. Distribution of other alleles is identical to other Caucasian populations.

The presence of the variant allele of MDR1 in exon 26 3435T was associated with statistically higher concentrations of amiodarone and its active metabolite. Statistically significantly higher drug concentrations were demonstrated even in the current presence of variant allele CYP2C8 * 3 and MDR1 3435T. These findings were confirmed by haplotype analysis, when in accordance with the literature, individuals with haplotype 12 had statistically significantly higher concentrations of the drug. In patients with amiodarone, we observed higher TSH values in the presence of two variant alleles in exon 26, 5,62 U/l versus 2,31 U/l in homozygotes with wild-type allele.

Our results of frequency of common MDR1 and CYP2C8 polymorphisms in the Czech population allow interpretation of clinical trial studies obtained in different populations and form basis for optimizing treatment with selected drugs.

Key words: amiodarone, cytochrome P450, CYP2C8, Czech population, MDR1, P-glycoprotein, pharmacogenetics, single nucleotide polymorphism