Summary

Drug metabolism is one of the key processes allowing to eliminate the administered dose. High interindividual variability of the activity of drug metabolizing enzymes is caused by many genetic and epigenetic factors. This variation can result in substantial differences in clinical response to the drug, ranging from failure of the therapy to appearance of toxic side effects or frequent onset of drug-drug interactions.

The aim of the thesis was to evaluate the influence of genetically determined variability in drug metabolizing enzymes activity on the drug pharmacokinetics, pharmacodynemics and to asses whether either phenotyping or genotyping can be effectively applied under the naturalistic conditions of routine clinical practice, for e.g. as a prediction tool during to asses individual risk of development and progress of a disease or to forecast the drug response. The thesis mainly summarizes previously published articles on the topic.

We have studied genetically determined variability of tramadol pharmacokinetics as well as drug-induced miosis in healthy volunteers with known CYP2D6 status. The lowest blood concentrations of principal active metabolite O-demethyltramadol accompanied by the highest levels of the parent compound at all sampling intervals up to 12 hours post-dose were found in the group of poor metabolizers (PMs) in comparison with intermediate (IMs) and extensive metabolizers (EMs). Our results suggest that the metabolic ratio of blood concentrations of tramadol/O-demethyltramadol could be used to distinguish PM and EM subjects with more than 99% confidence. Maximal values of drug-induced miosis (Emax) are partly overlapped among the genotype groups, but administration of tramadol lead to higher Emax than 1mm in none of the PMs.

Traditionally, CYP2D6 phenotype is examined by a metabolic ratio of cumulative excretion of debrisoquine and its metabolites in urine. We have studied the excretion of this compound in healthy volunteers with known CYP2D6 genotype. As expected, the administered dose is excreted in genotype-dependent manner, but we have found new, so far unknown metabolite 3,4-dehydrodebrisoquine that also displays genotype-dependent excretion. The inclusion of this new metabolite into the traditional metabolic ratio influences the results. It is however unknown, whether omitting of 3,4-dehydrodebrisoquine in the metabolic ratio leads to misclassification of PM subjects or not, and if so, what could be the frequency of this diagnostic mistake. The study also illustrates the possibilities of the most advanced analytical techniques in the pharmacogenetic scientific field.

We have also studied possible influence of liver cirrhosis on the metabolic ration of paraxanthin/caffeine in saliva as a phenotyping method to determine CYP1A2 activity. Metabolic ratio was significantly lower in patients than in healthy control subjects. It is therefore a suitable method to measure remaining metabolic capacity of the liver in this disease state.

Further we have studied, if deficiency in CYP2D active is a susceptibility factor for development or progression of familial adenomatous polyposis. The frequency of PMs in the group of patients did not differ substantially from that of healthy subjects, but the relatively small size of the group of patients with this rare disease does not allow to make fully conclusive conclusions. Nevertheless, higher metabolic ratio has been found in a subgroup of patients with malignant changes in the polypes in comparison to the patients without any malignancy during clinical examinations. This tendency can indicate influence of CYP2D6 activity on the progression of the disease.

Case reports demonstrating a crucial role of PM phenotype of thiopurinemethyltransferase (TPMT) on the development of serious myelotoxicity in patients receiving very small doses of azathiprine are included in the thesis as well. Bone marrow suppression was diagnosed in a young patient shortly after beginning of therapy with 50mg of azathioprine per day. Complete deficiency TPMT resulting in the occurrence of this side effect has been retrospectively proven by phenotyping and confirmed by detecting homozygous presence *TPMT*3A* allele in the genome.

It can be finally concluded, that the pharmacokinetics of some drugs and their pharmacodynamic effects are substantially dependent on the genotype of the drug metabolizing enzymes. The deficiency of the biotransformation activity can lead to onset of

serious adverse drug reactions. Phenotyping can be influenced by a presence of unknown metabolites of the probe substance, but in the same time it can be useful method to evaluate actual metabolism status of the liver, i.e. can be used to follow the liver disease progression. The knowledge about the activity of biotransformation processes prior to the drug exposure and subsequent individualization of the dosing can result in rationalization of pharmacotherapy.