PHARMACOGENETICS BASED THERAPEUTIC RECOMMENDATIONS – READY FOR CLINICAL PRACTICE?

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For many drugs, pharmacogenetic polymorphisms are known affecting biotransformation and clinical outcome. The clinical importance of these variants depends on allele-frequency and the effect size of the clinical outcome parameters. Further, it depends on the therapeutic range of the drug which is affected, on predictability of drug response as well as on duration until onset of therapeutic efficacy. Consequences which arise from genotyping might be: adjustment of dose according to genotype, choice of therapeutic strategy or even choice of drug.

In antidepressant drug treatment, most drugs are metabolized via the polymorphic cytochrome P450 enzymes CYP2D6 and CYP2C19. Huge differences in pharmacokinetic parameters have been consistently shown for many tricyclics, some SSRIs, and other antidepressant drugs. However, the effects on therapeutic efficacy and adverse events have been described controversially. Pharmacokinetic differences caused by genetic polymorphisms can be overcome by adapting the drug dosages and dosing intervals. Similar to bioequivalence studies, the aim to achieve similar plasma concentration time courses of antidepressants might help to reduce side effects and therapeutic failure.

In the field of antipsychotic drug treatment, genetic polymorphisms in drug metabolizing enzymes as well influence pharmacokinetic parameters to a large part. In these kinds of drug therapy, a more clear dose dependency of side effects such as extrapyramidal side effects exists, and the consideration of genetic polymorphisms might be more beneficial. Recent studies showed a relationship between the occurrence of adverse antipsychotic drug effects and *CYP2D6* genotype. A prospective evaluation of the cost-benefit of genotyping in this field would be very helpful for the aim of introducing pharmacogenetic diagnostic into drug therapy.

In cardiovascular disease, oral anticoagulants, beta-blockers, statins and other drugs such as phenytoin, losartan, and torsemide are affected by genetic polymorphisms of the cytochrome P450 drug metabolizing enzyme CYP2C9. Studies in patients or healthy volunteers revealed up to 10-fold differences in pharmacokinetic parameters such as oral clearance or elimination half-lives due to genetic polymorphisms of CYP2C9. For oral anti-diabetics, decreased oral clearances can lead to hypoglycemia, which is a severe adverse drug effect in diabetic patients. In oral anticoagulant therapy, CYP2C9 polymorphisms have already been shown to cause differences in anticoagulant efficacy measured by the INR ratio, which lead to differences in the frequency of bleeding complications. Nonsteroidal anti-inflammatory drugs have a high risk for gastrointestinal bleeding complications and ulcerations, and differences in pharmacokinetic parameters of these drugs caused by CYP2C9 polymorphisms might result in a higher risk for these adverse effects in individuals carrying genetic polymorphisms.

Data appear established enough for routine consideration of CYP genotypes in certain longterm drug therapies. Nevertheless, before routine genotyping can be incorporated into the clinical setting, the benefits of genotype-based therapeutic recommendations have to be tested by a randomized controlled clinical trial comparing therapy with pharmacogenetic diagnostics with *therapy as usual* in a randomized controlled fashion. The typical primary outcome parameters in such studies should be efficacy parameters and parameters like long-term outcome, adverse drug effects and direct cost-related parameters such as duration of hospital stay or disability.