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PHARMACOGENETICS AND ANTIPSYCHOTICS IN THE LIGHT OF PERSONALIZED PHARMACOTHERAPY

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SUMMARY

The concept of personalized drug therapy on the basis of genetic investigations has become a major issue in psychopharmacology. Pharmacogenetic studies have focused on polymorphisms in liver cytochrome P450 isoenzymes that metabolize many antidepressant and antipsychotic medications. The most significant results are the association between drug metabolic polymorphisms of cytochrome P450 with variations in drug metabolic rates and side effects. Additionally, polymorphisms in dopamine and serotonin receptor genes are repeatedly found associated with response phenotypes, probably reflecting the strong affinities that most antipsychotics display for these receptors. The contribution of kinetic factors to the clinical outcome of antipsychotic treatment has a strong evidence base. Genetic tests for the pretreatment prediction of antipsychotic response have obvious implications for the selection of most appropriate drug and dose and contribute for the optimization of antipsychotic treatment. The pretreatment determination of individual's drug metabolic rates by CYP genotyping is the leading field. This review summarizes the present knowledge of associations between cytochrome P450 isoenzymes and the efficacy and side effects of antipsychotics.

Key words: *pharamacogenetics – antipsychotics – polymorphisms - isoenzymes P450*

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Introduction

Antipsychotic drugs achieve a certain degree of clinical improvement in the treatment of psychosis in about 50% of schizophrenic patients (Miyamoto et al. 2005). Delay in finding an adequate treatment for psychosis has a detrimental effect on prognosis and chances of recovery. The nature of drug response is highly complex, involving clinical, genetic and environmental factors.

Because of these factors there are much interindividual variabilities in the treatment with antipsychotics. Genetic determination of patients' metabolic status is expected to bring clinical benefits by helping to adjust therapeutic doses and reduce adverse reactions (Arranz & de Leone 2007). The summary of this findings relevant for schizophrenia will be presented in this review.

Clinical and environmental factors

Response for example to the clozapine, may be influenced by clinical and demographic factors. Male gender and early age of onset predict poor response, whereas presence of EPS with previous treatments and paranoid symptoms predict good response to treatment with clozapine (Lieberman et al. 1996). Environmental factors such as cigarette smoking and diet can induce or inhibit metabolic pathways, which affects plasma levels of antipsychotic metabolites.

Therefore, the knowledge of patients eating and smoking habits can be used as an indicator for the adjustment of therapeutic doses (Nebert & Dieter 2000). Despite the fact that clinical and environmental factors, have small to moderate influence, together with genetic determinants of response, they should be considered when selecting treatments.

Pharmacokinetic factors

Genetic variants in Phase I and II enzymes are known to reduce or increase antipsychotic activity. Phase I oxidation reactions are involved in the metabolism of antipsychotic drugs. CYP enzymes show large interindividual differences in activities due to genetic variants constituting multialelic systems. These can be distinguished as poor, intermediate, extensive or ultra fast metabolizers (Bondy & Spellmann 2007). Mutant alleles differ from normal alleles by point mutations, gene deletions or gene duplications. The poor metabolizers have inactive allelic variant, intermediate metabolizers have at least one copy of an active gene and ultra fast metabolizers contain duplicated or amplified gene copies. Due to concentrations of drug could be increased or decreased. (Mihaljević-Peleš et al. 2008). There are also considerable differences in allele and genotype frequency across ethnic groups.

CYP2C19 may be clinically relevant for the metabolism of antidepressants and benzodiazepines but has small significance for antipsychotic treatment. CYP2D6 is the main metabolic pathway of many antidepressants and a number of classical antipsychotics (Bertilsson et al. 2002).

Table 1. CYP enzymes and alleles involved in antipsychotic metabolism and their substrates, inhibitors and inducers

CYP 450	Substrate	Inhibitor	Inducer	Polymorphism
1A2	Clozapine Olanzapine Duloxetine Mirtazapine Propranolol Teophylline Caffeine Clomipramine Estradiol	Fluvoxamine Cimetidine Ciprofloxacine Oral contraceptives Estrogens Severe respiratory tract infections	Cigarette smoke Brussel sprouts Omeprazole	CYP1A2*1C-↓ inducibility in smokers, CYP1A2*1F-↑ inducibility in smokers
2C9	Phenitoin Fluvastatin Ibuprofen Diclophenac Tolbutamide Warfarin Valproic acid	Fluvoxamine Fluoxetine (moderate inhibitor) Fluconazole	Prednisone Rifampicine	CYP2C9*2, *3-↓ activity, even up to 90%, polymorphism in 35% Caucasians
2C19	Amitryptiline Diazepam Moclobemide Omeprazole Pantoprazole Clomipramine Citalopram	Fluvoxamine Fluoxetine	Carbamazepine Rifampicine	3-5% Caucasians have no enzyme expression (CYP2C19*2 alelle)
2D6	Risperidone Haloperidol Fluphenazine Sertindole Aripiprazol Zuclopentixol Codeine Tramadol β-blockers Some antiarrhythmics (Flecainide) Olanzapine (minor pathway)	Fluoxetine Paroxetine Fluvoxamine and sertraline are weak inhibitors	Not inducible	5-10% Caucasians have no enzyme expression (mostly CYP2D6*4 alelle) or have multiple gene copies CYP2D6*2xN
3A4	Ziprasidone Quetiapine Sertindole (minor pathway) Aripiprazole Calcium antagonists Statins Macrolide antibiotics Alprazolam Carbamazepine Cinidine Cyclosporine Tacrolimus Tamoxifen Protease HIV-1inhibitors Testosterone	Fluvoxamine Clarythromycine	Carbamazepine Glucocorticoids Hyperphorine Phenobarbital Rifampicin	Limited data for existing polymorphisms

De Leon et al. 2005; Zanger et al. 2008; Brouwers et al. 2009

The gene coding for this enzyme is highly variable. Kirchheiner et al. have demonstrated that the metabolism of the haloperidol is severely reduced in PMs, and a reduced therapeutic dose should be used (Kirchheiner et al. 2004). At the other hand, CYP2D6 did not predict response to risperidone, but predicted metabolic ratios and side effects (de Leone et al. 2005). No association was found between CYP2D6 PM variants and clozapine response (Arranz et al. 1995). However, the incidence of tardive dyskinesia is higher in patient with inactive CYP2D6-alleles (Kapitany et al. 1998). CYP 1A2 is the main metabolic pathway of the antipsychotics clozapine and olanzapine and several polymorphisms have been reported in the CYP1A2 (Eirmann et al. 1997; Ring et al. 1996, Murayama et al. 2004). In addition, CYP1A2 polymorphisms did not

significantly influence individuals' clozapine metabolic capacity (Kootstra-Ros et al. 2005). In addition, smoking seriously affects the activity of CYP1A2. Smoking may result in reduced clozapine plasma levels, and an adjustment of therapeutic dose is recommended. The most important CYP enzymes and allele variants involved in antipsychotic phase I metabolism and their substrates, inhibitors and inducers are presented in table 1.

Although there are several variants of the CYP3A4 enzyme, involved in the metabolism of most antipsychotics, no significant associations of these variants with antipsychotic variability have been reported. There are also no significant response associations with the polymorphic CYP3A5, CYP2C9 and CYP2C19.

At the end, phase II enzymes, which are responsible for the inactivation of drug metabolites via conjugation have not been extensively investigated. This is, however, an important area for future research.

CONCLUSION

The aim of pharamacogenetics is to help clinicians to choose the best treatment for each individual patient. Genotyping CYP2D6 is proposed to improve drug dosing in the individual patient: Individualizing dose escalation schemes have been developed both for antidepressants and antipsychotics, which are based on the distinction of PM, UM and others. Depending on the impact of the CYP2D6-enzyme activity on the metabolism of a specific drug, dosage recommendations propose to prescribe 30–70% dose reduction on PM and 135–180% dose elevation in UM patients (Maier & Zobel 2008).

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