PHARMACOGENETIC AND PHARMACOLOGICAL TREATMENT IN PSYCHIATRIC PATIENTS

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Abstract

Brief introduction: Psychiatric medications metabolized by cytochrome 2D6, may lead to different clinical response, according to patient genetic profiles. Literature's data show that caucasian population is divided in 7% as poor metabolizer, 36% intermediate metabolizer, 50% extensive and 7% ultrarapid metabolizer [1]. The aim of the study is to understand the effects of different metabolic genotype in terms of clinical effectiveness.

Materials and methods: We enrolled 80 psychiatric patients, 38 males and 42 females, mean age at baseline time 43.7 years (range 17-78 years) with a diagnosis of panic disorder (16), mood disorders (36), mood disorders in comorbidity with panic disorders (21) or psychotic disorders (7). All patients were assessed with psychiatric evaluation and treated with psychopharmacological therapy (mood stabilizers, antipsychotics, antidepressants). They were subjected to a genotype analysis in order to evaluate the frequency of the allelic polymorphism of CYP2D6. The genotyping was performed through a DNA amplification technique (PCR) and a microarray technology INFINTY BioFilmChip.

Conclusions: The metabolic genotype of cytochrome 2D6 is directly linked to pharmacotherapy's effectiveness. Poor metabolizers (5% of our sample) showed only side effects and no benefits of the pharmacological treatment. Intermediate metabolizers were 31%; they more likely can develop adverse reactions to polypharmacotherapy and show an incomplete clinical response. Pharmacotherapy shows the best effectiveness in extensive metabolizers (59% in our population). Ultra rapid metabolizers (5% of our sample) had an insufficient clinical response. Testing metabolic genotype of 2D6 in clinical practice could allow us to avoid the onset of side effects and the risk of toxicity as well as recurrent dose corrections and therapy's failure. Moreover, patient's genotyping could help us to customize therapies in terms of doses and times on the basis of patient's genetic profile. Future, larger studies including also pharmacokinetics interactions, patient's compliance and race's genetic differences are warranted to better customize pharmacological therapies.

Key words: cytochrome 2D6, metabolic genotype, poor metabolizer, intermediate metabolizer, extensive, ultrarapid metabolizer

Introduction

Cytochromes are heme proteins, primarily responsible for the generation of ATP via electron transport. Several kinds of cytochrome exist and can be distinguished by spectroscopy (cytochromes a, b and d). A completely distinct family of cytochromes is known as the Cytochrome P450 (CYP450). CYPs metabolize thousands of endogenous and exogenous chemicals. In nature there are more than 200 P450 enzymes, of which 40 have been identified in humans. Six isoenzymes are responsible for at least 90% of enzymatic activity of the CYP450 (1A2, 3A4, 2C9, 2C19, 2D6, 2E1) [1][2] and Cytochromes 2D6 (CYP2D6) is one of the most studied in relation to genetic polymorphism. CYP2D6 gene

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(located on chromosome 22) has been reported to have more than 30 polymorphisms. This enzyme metabolizes approximately 25% of the drugs currently used. Psychiatric medications metabolized by cytochrome 2D6, may lead to different clinical response, according to patient genetic profiles. Several studies show that caucasian population is divided in different groups: 7% are poor metabolizers (having homozygous or heterozygous mutation leading to a lack of the enzyme in the liver), 36% are intermediate metabolizer (having a mutant allele and a functional allele of the gene, they are individuals who have a high risk of adverse reactions to the drug), 50% are extensive metabolizers (both alleles of the gene are active, it represents the percentage of normal individuals) and 7% are ultrarapid metabolizer (they show gene duplications with three or more functional alleles responsible for an increased expression of the gene, they are unlikely to benefit from the expected therapeutic effects) [1]. There is considerable variability in the distribution of CY2D6 among the different ethnical groups. The aim of the study is to understand the effects of different metabolic genotypes in terms of clinical effectiveness.

Materials and methods

We enrolled 80 psychiatric patients, 38 males, mean age at baseline time 43.7 years (range 17-78 years) with a diagnosis of panic disorder (n = 16), mood disorders (n = 36), mood disorders in comorbidity with panic disorders (n = 21) or psychotic disorders (n = 7). All patients were assessed with psychiatric evaluation and treated with psychopharmacological therapy (mood stabilizers, antipsychotics, antidepressants). They were subjected to a genotype analysis in order to evaluate the frequency of the allelic polymorphism of CYP2D6. The genotypic test was performed through a DNA amplification technique (PCR) and a microarray technology INFINTY BioFilmChip.

Results

We found that our sample was composed by 59% of extensive metabolizers (60% having significant side effects, 21% having good response and 19% therapeutic ineffectiveness). The 5% of our patients were poor metabolizers, the 25% of them having no benefits from pharmacological treatment, and the 75% presenting only side effects (hyperprolactinemia, weight gain, nausea, agitation). The clinical conditions of this group of patients improved by reducing drug doses. The 32% were founded to be intermediate metabolizers, with variable drug responses: the 64% of them showed side effects, the 28% had a therapeutic failure (these patients were all treated with carbamazepine and/or valproate, both acting as inducers of CYP3A4 substrates, thereby influencing the metabolism of alter substrate molecules of this isoenzyme) and just the 8% achieved a good response to therapy. This variability could be explained by several factors as personality, pharmacological interactions and compliance to therapy. Finally, the 5% were ultra rapid metabolizers, half of them having no benefits from the pharmacological treatment and the other half showing only side effects.

CYP2D6 Phenotype distribution in our sample

Poor Metabolizers (PM)	n. 4
Intermediate Metabolizers (IM)	n. 25
Extensive Metabolizers (EM)	n. 47
Ultrarapid Metabolizers (UM)	n. 4

Conclusions

The metabolic genotype of CYP2D6 is directly linked to pharmacotherapy's effectiveness.

The results show a good correlation between genotype and clinical phenotype in all groups except for extensive metabolizers (60% of this group developing major side effects). This result may be due to pharmacokinetic interactions between drugs able to induce or inhibit the specific isoenzyme when patients are treated with polypharmacy [3] and to the high prevalence (46%) of patients with anxiety disorder linked to farmacofobia (having an increased subjective perception of side effects). Testing metabolic genotype of 2D6 in clinical practice could allow us to avoid the onset of side effects and the risk of toxicity as well as recurrent dose corrections and therapy's failure. Moreover, patient's genotyping could help us to customize and personalize therapies in terms of doses evaluating patient's genetic profile. Future, larger studies including also pharmacokinetics interactions, patient's compliance and race's genetic differences are warranted to better customize pharmacological therapies. In the future, in order to have a more comprehensive understanding of the clinical response, it would be helpful to determine the plasma levels of active drug compounds in each patient, relating pharmacokinetic parameters to genotypic characterization. It may allow us to predict the clinical response in that specific patient after drug administration.

Take home messages for psychiatric care

- Psychiatric medications metabolized by cytochrome 2D6, may lead to different clinical response, according to patient genetic profiles
- Patient's genotyping could help us to customize therapies in terms of doses and times on the basis of patient's genetic profile
- Testing metabolic genotype of 2D6 in clinical practice could allow us to avoid the onset of side effects and the risk of toxicity as well as recurrent dose corrections and therapy's failure

References

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