Ned Tijdschr Klin Chem 2001; 26: 195-196

Genotyping in psychiatric patients: an overview

J. van der WEIDE[1] and L.S.W. STEIJNS[2]

The cytochrome-P450 (CYP) enzymes CYP2D6 and CYP2C19 are involved in the oxidative metabolism of numerous commonly prescribed psychoactive drugs, including many antidepressants and antipsychotics (1,2). Both CYP enzymes are genetically polymorphic. Several mutant alleles are known, associated with enzyme activities ranging from ultrafast to a complete absence. Therefore, metabolic capacity varies from one person to another, leading to variable drug excretion rates and intersubject differences in the final plasma drug concentrations. For this reason, therapeutic response and side effects vary widely between patients treated with the same dose of drug (3). Genotyping involves identification of defined genetic mutations on the *CYP* genes that give rise to a specific drug metabolism phenotype. By screening for genetic variants, every individual can be classified as either a poor (PM), an extensive (EM) or an ultrarapid metabolizer (UM), based on the number of functional genes present. In general, PMs will develop higher plasma drug concentrations in comparison with EMs, causing an increased risk of side effects and toxicity when subjected to standard recommended doses. UMs, on the other hand, will not reach therapeutic plasma levels upon treatment with standard doses, leading to therapeutic failure and false accusation of non-compliance (1). Identification of PM and UM subjects particularly is of clinical importance for adjustment of doses or changing medication in drug therapy, to assure therapeutic efficacy with a minimum risk of adverse effects (4).

METHODS

In our psychiatric hospital we have been performing *CYP* genotyping for identification of PMs and UMs routinely since 1997. The standard procedure is depicted schematically in figure 1. Every newly admitted patient is screened for the three most common defective allelic variants of *CYP2D6* (i.e. *CYP2D6*3*, **4* and **5*), the *CYP2D6* gene duplication and the non-functional *CYP2C19*2* allele. In Caucasian populations this allows identification of about 95% and 80% of poor metabolization caused by 2D6 and 2C19 enzyme deficiency, respectively. The sensitivity of the *2D6* gene duplication test for detection of the UM phenotype is only about 10-30% (5,6).

The majority of patients start with psychoactive drug therapy on admission and after 30 days plasma drug concentrations are measured. When the concentration exceeds the therapeutic index by 10% or more, the patients genotypical state, drug dose and (co)medication are considered by the clinical chemist, in consultation with the pharmacist and an advice is given to the physician. When the drug concentration/dose (C/D) ratio is still abnormal after dose adjustment and/or changing medication, while no aberrant genotype was detected with the allelic variants mentioned above, the patient is screened for the less common defect gene variants of *CYP2D6* (i.e. *CYP2D6*6*, **7*, **8*, **11*, **12* and **14*) and *CYP2C19* (*CYP2C19*3*, **4* and **5*). By this additional screening, poor metabolism is detectable with respectively close to 100% (2D6) and about 86% accuracy (2C19). Most of the allelic variants can be detected by fast and easy assays based on polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) techniques (7).

Table 1. Genotype frequencies found by routine genotyping in 1880 patients

Genotype	Prevalence n (%)	Number of functional genes	Phenotype
CYP2D6			
**1/*1x2*	56 (3.0)	3	UM
**4/*1x2*	13 (0.7)	2	EM
**1/*1*	1041 (55.3)	2	EM
**1/*3*	60 (3.2)	1	EM
**1/*4*	562 (29.9)	1	EM
**1/*4x2*	7 (0.4)	1	EM
**3/*4*	11 (0.6)	0	PM
**3/*3*	6 (0.3)	0	PM
**4/*4*	117 (6.2)	0	PM
**4/*4x2*	7 (0.4)	0	PM
CYP2C19			
**1/*1*	1400 (74.4)	2	EM
**1/*2*	439 (23.4)	1	EM
**2/*2*	41 (2.2)	0	PM

The *CYP2D6*5* allele is only detected in case of homozygousity (genotype **5/*5*; not present in our sample).

Department of Clinical Chemistry, St. Jansdal Hospital, Harderwijk[1]; Department of Clinical Chemistry, Psychiatric Hospital Meerkanten, Ermelo[2]

Correspondence to: Dr J. van der Weide, St Jansdal Hospital, Department of Clinical Chemistry, PO Box 138, 3840 AC Harderwijk. e-mail: j.vander.weide@stjansdal.nl

Poster presented at the 54th NVKC Congress in Lunteren on 11.04.01.

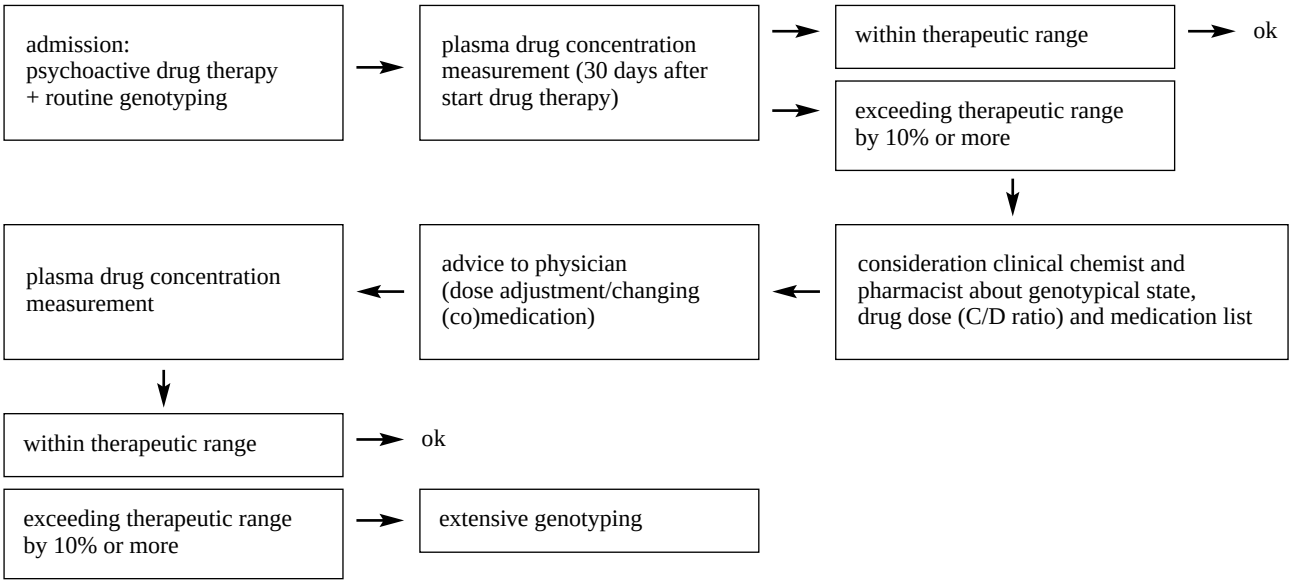

Figure 1. Flow chart for genotyping on admission

RESULTS

About 1000 patients are admitted into our hospital every year, of whom about half have been admitted (and genotyped) before. Since genotyping needs to be done only once in a lifetime, about 500 patients are screened on a yearly basis. PMs and UMs are found with prevalences of 9.7 and 3.0%, respectively. This is comparable to the frequencies reported in other studies of Caucasian populations (1, 5, 8). Table 1 shows the distribution of the individual *CYP2D6* and *CYP2C19* genotypes, found by routine screening of 1880 psychiatric patients consecutively admitted between 01-01-1997 and 01-01-2000.

In our hospital, a therapeutic plasma-drug level is reached in almost every patient after drug selection and/or dose adjustment based upon genotypical state. However, the clinical significance of a specific *CYP* genotype for a specific drug in an individual patient is not always clear and depends on several factors. Some of these factors are drug related, like the width of the therapeutic range of the drug, the activity of the metabolites, the contribution of the polymorphic enzyme to the elimination of the drug and the possibility of alternative excretion pathways. Other factors are patient related, like age, gender, disease state and environmental factors such as smoking, nutrition, alcohol and the use of comedication (9).

CONCLUSIONS

After 3 years of experience we can conclude that *CYP2D6* and *CYP2C19* genotyping, performed routinely in every patient after admission into a psychiatric hospital, is a good help in individualization and optimization of pharmacotherapy. Quite often the procedure facilitates and accelerates a proper adjustment to psychoactive drugs, which improves the quality of patient care. Genotyping is rather easy to perform; it can be done within 24 h and the method requires only a small blood sample. Of course there is a considerable cost associated with this routine screening procedure: about $100 per patient. On the other hand, treatment expenses are reduced. Therapeutic efficiency is increased in a number of patients, which means less toxic episodes or therapeutic failure and subsequent intervention (10). Compared with other psychiatric hospitals, overall no extra costs are associated with this practice.

Literature

1. Coutts RT, Urichuk LJ. Polymorphic cytochromes P450 and drugs used in psychiatry. Cell Mol Neur 1999; 19: 325-354.
2. Dahl ML, Sjöqvist F. Pharmacogenetic methods as a complement to therapeutic monitoring of antidepressants and neuroleptics. Ther Drug Monit 2000; 22: 114-117.
3. Weide J van der, Steijns LSW. Cytochrome P450 enzyme system: genetic polymorphisms and impact on clinical pharmacology. Ann Clin Biochem 1999; 36: 722-729.
4. Griese EU, Zanger UM, Brudermanns U, et al. Assessment of the predictive power of genotypes for the in-vivo catalytic function of CYP2D6 in a German population. Pharmacogenetics 1998; 8: 15-26.
5. Sachse C, Brockmöller J, Bauer S, Roots I. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. Am J Hum Genet 1997; 60: 284-295.
6. Ferguson RJ, DeMorais SM, Benhamou S, et al. A new genetic defect in human CYP2C19: mutation of the initiation codon is responsible for poor metabolism of S-mephenytoin. J Pharmacol Exp Ther 1998; 284: 356-361.
7. Marez D, Legrand M, Sabbagh N, et al. Polymorphism of the cytochrome P450 CYP2D6 gene in a European population: characterization of 48 mutations and 53 alleles, their frequencies and evolution. Pharmacogenetics 1997; 7: 193-202.
8. Poolsup N, Li Wan Po A, Knight TL. Pharmacogenetics and psychopharmacotherapy. J Clin Pharm Ther 2000; 25: 197-200.
9. Weide J van der, Weelden MJM van, Steijns LSW. Genotypering bij psychiatrische behandeling: is het echt bruikbaar? Ned Tijdschr Klin Chem 1999; 24: 223-228.
10. Chou WH, Yan FX, Leon J de, et al. Extension of a pilot study: impact from the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. J Clin Psychopharmacol 2000; 20: 246-251.