Pilot Study of the Cytochrome P450-2D6 Genotype in a Psychiatric State Hospital

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Objective: The authors conducted a pilot study to develop preliminary data on the frequency of cytochrome P450-2D6 (CYP2D6) genotypes in state psychiatric hospital patients and to establish population sizes needed to determine potential clinical relevance in therapeutic outcome. **Method:** One hundred consecutive inpatients at Eastern State Hospital in Kentucky who provided informed consent were genotyped at the CYP2D6 locus during their hospital stay. **Results:** Twelve of the patients were CYP2D6 deficient, and four carried the *1Xn or *2Xn allele associated with ultrarapid metabolism; all of these patients were Caucasian (N=87). The rate of deficiency in CYP2D6 expression in these Caucasian state psychiatric hospital patients (14%) was twice that of the U.S. population (7%). The patients with CYP2D6 deficiency also appeared more likely to experience side effects in response to CYP2D6 medications. **Conclusions:** This study, limited by a small number of subjects, suggests that one-fifth of Caucasians admitted to a state hospital in Kentucky had genotypes associated with extremes in CYP2D6 activity that may have affected their response to CYP2D6 medications.

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The cytochrome P450-2D6 (CYP2D6) is involved in the metabolism of many antipsychotic medications (many typical compounds and risperidone), most tricyclic antidepressants, some selective serotonin reuptake inhibitors, some other antidepressants (venlafaxine and the *m*-chlorophenylpiperazine metabolite of nefazodone and trazodone), β blockers, antiarrythmics, and opiates (1). Phenotyping studies in the United States and Europe suggest that approximately 7% of Caucasians are poor metabolizers and deficient in CYP2D6 expression (2). The proportion in subjects of African and Asian heritage is 1% to 3%. Any combination of nonfunctioning recessive alleles is associated with lack of CYP2D6 activity. Extensive (or normal) metabolizers have one or two wild type alleles (2). Extensive metabolizers may be converted to phenotypic poor metabolizers by competitive inhibition (fluoxetine and paroxetine in clinical doses) (1). Average doses of CYP2D6 medications may be associated with toxic concentrations in deficient subjects. The relationship between the CYP2D6 genotype and psychotropic side effects has not been well studied. Three previous studies included five poor metabolizers taking antipsychotics (3, 4) and four taking antidepressants (2).

The *1Xn allele and the *2Xn allele have been described in low frequencies in European samples (1%–7%) (5). Subjects with more than two copies of these alleles are ultrarapid CYP2D6 metabolizers.

METHOD

Eastern State Hospital in Lexington, Ky., has approximately 1,600 admissions per year and serves as the primary psychiatric hospital for one-third of the state. In October 1996, all admitted patients were offered free CYP2D6 genotyping until 100 consecutive patients provided written informed consent after receiving a complete description of the study. Instruments for assessment of side effects included the Simpson-Angus Rating Scale (6) and the *Udvalg for Kliniske Undersøgelser* (UKU) Side Effect Rating Scale (7). Blood (10 ml) was collected and processed by polymerase chain reaction

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TABLE 1. Medication History of Caucasian State Hospital Inpatients With CYP2D6 Deficiency (N=12) or *1Xn or *2Xn Allele (N=4)

Group and History	Number of Patients
Inpatients with CYP2D6 deficiency	12
Never taken CYP2D6 medications	1
Taken CYP2D6 medications	11
No side effects from trazodone or nefazodone	3
Trazodone[a] (one dose of 50 mg)	1
Nefazodone[a] (300 mg/day); patient had stopped taking fluoxetine[a] (hot flashes, insomnia, and anorexia) and thioridazine[a] ("too slow") after a few days each	1
Nefazodone[a] (200 mg/day)	1
Problems with other antidepressants	3
Sertraline and venlafaxine[a] were discontinued	1
Doxepin[a] was added to paroxetine[a] but stopped after one dose because of sleepiness	1
Paroxetine[a] (patient experienced jitteriness); fluoxetine[a] and paroxetine[a] had been stopped before	1
Problems with antipsychotics	5
Risperidone[a] (9 mg/day) and venlafaxine[a] (112.5 mg/day); risperidone was stopped because of severe sedation	1
Risperidone[a] (3 mg/day) and propranolol[a] (30 mg/day); patient had akathisia, concentration difficulties, and sleepiness; noncompliance and readmission 1 month later	1
Haloperidol[a] (5 mg/day); patient experienced akathisia; patient had discontinued paroxetine[a] in the past	1
Risperidone[a] (3 mg/day) and nefazodone[a] (300 mg/day); patient experienced many side effects (nervousness, palpitations, diminished sexual drive, and weight gain)	1
Perphenazine[a] (4 mg/day) (patient experienced stiffness); patient had history of neuroleptic malignant syndrome with haloperidol[a]	1
Subjects with *1Xn or *2Xn allele	4
Bipolar patient treated with lithium, metoprolol,[a] and haloperidol[a] (oral 10 mg/day and decanoate 150 mg/4 weeks); low haloperidol level (4.7 ng/ml); past side effects from fluoxetine[a]	1
Depressive patient refused antidepressants; paroxetine,[a] fluoxetine,[a] venlafaxine,[a] imipramine,[a] and sertraline have not helped him	1
Depressive patient started on regimen of desipramine[a] (50 mg/day); patient had stopped paroxetine[a] because of weight gain	1
Bipolar patient taking lithium and thiothixene	1

[a] Known CYP2D6 substrate; *m*-chlorophenylpiperazine, a metabolite of trazodone and nefazodone, is a CYP2D6 substrate.

for *3,*4,*5, *7, *6, *1Xn, *2Xn, and *4Xn alleles (2). The computerized statistical program Power was used (with one-tailed alpha=0.05) to establish the population sizes needed to determine differences between poor and extensive metabolizers in therapeutic outcome.

RESULTS

Of the 100 patients, 52 were men and 48 were women; 87 were Caucasian, 12 were African American, and one was classified as other. The patients' mean age was 36.5 years (SD=9.2). The DSM-IV diagnoses assigned by treating psychiatrists included mood disorders (N=41), schizophrenia and other psychotic disorders (N=28), and other diagnoses (N=31). On admission, 72 of the patients were taking at least one drug metabolized by the CYP2D6; 10 were taking two CYP2D6 substrates, and 11 were taking an inhibitor of the CYP2D6 substrate and at least one other CYP2D6 substrate.

Twelve patients were CYP2D6 deficient; all of these patients were Caucasian (95% confidence interval=7.3%–23%) (table 1). One CYP2D6-deficient patient had never taken psychiatric medications; three did not have side effects while taking trazodone or nefazodone, but one of these three had discontinued two CYP2D6 medications in the past. Three CYP2D6-deficient patients experienced substantial side effects, and their antidepressants were switched during their short hospital stays (mean=6 days). Five CYP2D6-deficient patients experienced substantial side effects while taking antipsychotic medications.

On admission, seven of 10 CYP2D6-deficient patients taking CYP2D6 medications had at least moderate side effects according to the UKU Side Effect Rating Scale or the Simpson-Angus Rating Scale (95% confidence interval=35%–93%); 28 (46%) of 61 extensive metabolizers taking CYP2D6 medications had side effects (95% confidence interval=33%–59%). A larger naturalistic study with 300 patients (power=0.81) or even with 500 patients (power=0.95) would be needed to establish a significant difference between patients who were or were not CYP2D6 deficient. This comparison is limited by the inclusion of all medications known to be metabolized by CYP2D6 and of patients taking more than one CYP2D6 substrate. CYP2D6 may play a minor role in some drug metabolism.

To increase homogeneity, we also performed an analysis of drugs believed to be dependent on CYP2D6 metabolism (perphenazine, thioridazine, risperidone, chlorpromazine, haloperidol, nortriptyline, desipramine, and amitriptyline). All five poor metabolizers (95% confidence interval=48%–100%) and 17 (47%) of 36 extensive metabolizers (95% confidence interval=30%–64%) experienced side effects while taking drugs heavily dependent on CYP2D6. This comparison almost reached significance (p=0.05, two-tailed Fisher exact test). Additionally, extensive metabolizers taking several substrates or a substrate and an inhibi-

tor may behave as phenotypic poor metabolizers, decreasing the influence of the genotype.

Four of the patients had the 2Xn allele; all were Caucasian (95% confidence interval=1%–11%). One depressive patient refused antidepressant medication, saying that antidepressants never helped him in the past, and one patient with bipolar disorder had relatively low haloperidol levels (table 1).

DISCUSSION

In the United States, phenotyping studies suggest that CYP2D6 deficiency is present in 7% of the population, but genotyping studies are needed. This pilot study suggests that CYP2D6 deficiency may be overrepresented in Caucasians who are admitted to psychiatric hospitals (14%). The 7% figure is close to the lower limit (7.3%) of the 95% confidence interval for 14%. If this trend with borderline significance is verified in a larger sample, there would be two possible explanations: 1) CYP2D6 is associated with severe mental illness or 2) CYP2D6 is associated with a greater risk for hospital admissions. A European study suggested that severe mental illness is not related to CYP2D6 genotype (8). Although not statistically significant because of the small number of subjects, the findings of the current study suggests that CYP2D6 deficiency may be associated with more medication side effects and subsequently with noncompliance and rehospitalizations.

A larger naturalistic study (N=300 to N=500) is needed to establish statistically significant differences in medication side effects between extensive and poor metabolizers; a study including all CYP2D6 substrates will permit generalization of the results. A more homogeneous and smaller study may verify a significant difference only in those patients taking medications dependent on CYP2D6 metabolism (N=150 will have a power of 0.91). The effect of genotype may be even stronger in patients taking only one CYP2D6 substrate, but the reduced number of poor metabolizers makes it impossible to make power estimations for such a study.

The frequency of the *1Xn or *2Xn allele in the current study (5%) was comparable to what has been found in European Caucasians (1%–7%). Currently, our methodology cannot establish the number of copies of this allele. Subjects with more than two copies are ultrarapid metabolizers. Knowledge of the CYP2D6 genotype should allow psychiatrists to identify patients who do not do well with average doses. One-fifth of Caucasians admitted to state hospitals may have genotypes associated with extreme CYP2D6 activity and need a differential pharmacological approach. CYP2D6-deficient patients may need drugs not metabolized by CYP2D6 or very low doses of CYP2D6 substrates. Ultrarapid metabolizers may need drugs not metabolized by CYP2D6 or high doses of CYP2D6 substrates. This pilot study shows that it is possible to establish a screening program in a busy state hospital and that research in this neglected area is needed.

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