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CYP2D6 genotype and antipsychotic-induced extrapyramidal side effects in schizophrenic patients

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Abstract *Objective*: In order to evaluate whether poor metabolizers (PM) of debrisoquine are overrepresented among patients with acute dystonic reactions and chronic movement disorders associated with the administration of antipsychotic drugs, the *CYP2D6* genotype was determined in schizophrenic patients.
Methods: Allele status for *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, and *CYP2D6*6* as well as gene duplication was determined by allele-specific PCR, long-PCR and restriction fragment length polymorphism analysis (RFLP) in 119 schizophrenic patients (99 males and 20 females). All subjects were treated with antipsychotics metabolized, at least partially, by this isozyme. Sixty-three of the patients (52.9%) had a history of extrapyramidal side effects (EPS), while 56 (47.1%) had not experienced such problems (controls).
Results: Sixty-five patients (54.6%) were homozygous for a functional *CYP2D6*1* allele, 44 (37.0%) were heterozygous for detrimental alleles, and 4 (3.4%), who carried two detrimental alleles, were classified as PM. In six patients (5.0%) duplication of a functional *CYP2D6* gene was found, and they were consequently classified as ultrarapid metabolizers (UM). Homo- and heterozygous extensive metabolizers (EM) as well as UM were equally distributed between patients with and without EPS, whereas all the PM had a history of EPS. No significant differences in allele frequencies between the two groups were found.
Conclusion: Although the results cannot be considered conclusive due to the small number of PM patients in our study, the PM genotype may be a predisposing factor for antipsychotic-induced EPS. Knowledge of the *CYP2D6* genotype, before starting antipsychotic therapy, might be useful in identifying subjects at risk of developing EPS.

Key words *CYP2D6* · Genotype · Antipsychotic drugs · Extrapyramidal side effects

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Introduction

The use of antipsychotic drugs in the treatment of schizophrenia is associated with extrapyramidal side effects (EPS), such as acute dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia [1, 2]. They occur in a majority of patients receiving traditional antipsychotics, while the risk for EPS appears to be lower with newer compounds [3]. Dopamine receptor blockade in the basal ganglia is believed to be the underlying mechanism of EPS [4].

Many studies have aimed to identify potential risk factors of developing severe EPS, but the results have been controversial [5, 6, 7, 8]. It has been suggested [9] that the high frequency of dyskinesia among schizophrenic patients might be related not only to the antipsychotic therapy, but also to the pathophysiology of the psychiatric disorder.

EPS appear to be related to the antipsychotic dosage, and, consequently, to the plasma concentrations of the drug, since lower doses produce fewer EPS than moderate to high doses [4]. Therefore, every factor which might contribute to high drug plasma levels may increase the risk of EPS. It has been shown that impaired

drug metabolism may play a crucial role in the incidence and spectrum of concentration-dependent side effects [10]. EPS could thus be related to the patient's metabolic capacity, whose influence on drug plasma levels is well established.

Most antipsychotics, including perphenazine, thioridazine, haloperidol, and zuclopenthixol, are eliminated, at least partially, by oxidative metabolism catalyzed by a specific hepatic cytochrome P-450 isozyme (CYP), CYP2D6 [11, 12, 13, 14, 15]. This enzyme exhibits genetic polymorphism, due to the presence of a large number of functionally important allelic variants of the *CYP2D6* gene [16]. Individuals with deficient enzyme activity are classified as poor metabolizers (PM) and carry two detrimental *CYP2D6* alleles, while the rest, with at least one functional gene, are termed extensive metabolizers (EM) [17, 18, 19]. The PM phenotype is inherited as an autosomal recessive trait [20, 21] and occurs in European populations with a prevalence ranging from 3% to 10% [22].

Interindividual differences in the elimination kinetics and in steady-state plasma concentrations of antipsychotics resulting from genetically determined variability in the expression of CYP2D6 may thus have important clinical implications [15]. An association between the PM phenotype and acute antipsychotic-induced adverse effects has been documented in a few patients [23, 24]. In schizophrenic patients with tardive dyskinesia, no overrepresentation of PM was found, but it was suggested that the CYP2D6 metabolic capacity might influence the severity of EPS [25]. The results of two other studies [26, 27] indicate that the *CYP2D6* PM genotype may be a contributing factor to antipsychotic-induced EPS, including tardive dyskinesia.

The aim of the present study was to evaluate the possible association between the *CYP2D6* genotype and the appearance of antipsychotic-induced EPS and particularly to verify whether a genetically impaired metabolic capacity (i.e., the PM status) is related to a higher risk for EPS in schizophrenic patients during long-term therapy with antipsychotics metabolized by this enzyme.

Patients and methods

Patients

Among schizophrenic patients resident in a long-term psychiatric unit in Messina, Italy, a total of 119 subjects, 99 males and 20 females, aged 25–75 years (mean age ± SD, 50 ± 12), were recruited in the study, which was performed during 1997. In order to be included, patients had to be diagnosed as suffering from schizophrenic disorders according to the DSM IV criteria and treated with antipsychotic drugs metabolized at least partially by CYP2D6. Patients treated with antipsychotic drugs not metabolized primarily by CYP2D6, such as clozapine (18 patients) or substituted benzamides (12 patients) were excluded. No patient was receiving risperidone, an antipsychotic predominantly metabolized via CYP2D6 [28], as this agent was not available in the psychiatric unit at the time of study. Sixteen patients with concomitant organic disorders or receiving no antipsychotic medication were not considered for the study. The diagnoses of the included patients were paranoid schizophrenia in 46 cases, disorganized schizophrenia in 32, undifferentiated schizophrenia in 28, catatonic schizophrenia in 4 and residual schizophrenia in 9 cases. The participating patients had been continuously treated with antipsychotic drugs from 5 to 27 years (mean ± SD exposure time, 17.5 ± 5.5 years). Of the patients, 39 were in therapy with haloperidol, 12 with haloperidol decanoate, 10 with perphenazine, 15 with levomepromazine, 6 with fluphenazine decanoate, 9 with chlorpromazine, 23 with thioridazine, and 22 with zuclopentixol, 16 patients receiving two antipsychotics in association. All subjects, of European Caucasian origin, were otherwise in good physical health. Patients underwent neurological examination to evaluate the presence of EPS and their medical records were reviewed to recognize the occurrence of previous antipsychotic-induced acute dystonic reactions. Parkinsonism was assessed by using the Simpson-Angus Scale (SAS), while tardive dyskinesia was rated using the Abnormal Involuntary Movement Scale (AIMS). Admittedly, as all patients were receiving antipsychotics at the time of the investigation, tardive dyskinesia might have been masked in some patients. Sixty-three patients (52.9%) were included in the group of patients with EPS, having actual extrapyramidal symptoms and/or a history of movement disorders, while 56 patients (47.1%), with no such problems at the time of the study or earlier as assessed by the medical history, constituted the control group. In the group with EPS, acute dystonia was present in 23 patients, parkinsonism in 37, and tardive dyskinesia in 15. Twelve patients had experienced two or more different EPS. Thirty-six patients with EPS (but none in the control group) also received anticholinergic drugs (biperiden, orphenadrine, or trihexiphenidyl) in order to treat parkinsonism or to prevent reappearance of acute dystonia. As shown in Table 1, the two groups were homogenous with respect to the number of patients and to demographic and drug exposure characteristics, including drug dosage. Dose comparison between the antipsychotic compounds was made by converting antipsychotic doses to chlorpromazine equivalents [29].

The protocol was approved by the Ethics Committee at the Azienda Sanitaria Locale 5, Messina, Italy, and written informed consent to participate in the study was obtained from the patients or their relatives.

Genotyping methods

For the determination of the *CYP2D6* genotype, a 10-ml blood sample was obtained from each subject and kept frozen at −20 °C.

Table 1. Characteristics of the patients with and without extrapyramidal side effects (*EPS*)

	Control patients ($n = 56$)	Patients with EPS ($n = 63$)
Sex (M/F)	48/8	51/12
Age[a] (years)	51 (12)	49 (12)
Diagnosis		
Paranoid schizophrenia	21	25
Disorganized schizophrenia	10	22
Undifferentiated schizophrenia	17	11
Catatonic schizophrenia	0	4
Residual schizophrenia	8	1
Antipsychotic intake[a] (mg/day chlorpromazine equivalents)[b]	322 (105)	309 (112)
Antipsychotic exposure[a] (years)	17.3 (5.4)	17.5 (5.5)
Pharmacotherapy		
Butyrophenones	19	32
Phenothiazines	32	29
Thioxanthenes	9	13
Anticholinergics	0	36

[a] Age, antipsychotic intake, and antipsychotic exposure are given as mean (SD in parentheses)
[b] During the year before evaluation of EPS

Table 2 *CYP2D6* genotype and allele frequencies in patients with extrapyramidal side effects (*EPS*) and control patients (%)

	Predicted phenotype	Controls ($n = 56$)	Patients with EPS ($n = 63$)
Genotype			
**1/*2 × 2*	UM	3 (5.4)	3 (4.8)
**1/*1*	EM homozygous	32 (57.1)	33 (52.4)
**1/*3, *1/*4, *1/*5, *1/*6 or *2 × 2/*4*[a]	EM heterozygous	21 (37.5)	23 (36.5)
**4/*4 or *4/*5*	PM	0	4 (6.3)
Alleles			
**1*		87/112 (77.7)	89/126 (70.6)
**3*, **4*, **5* or **6*		21/112 (18.7)	31/126 (24.6)
**2 × 2*		3/112 (2.7)	3/126 (2.4)
**2 × 2* or **4 × 2*		1/112 (0.9)	3/126 (2.4)

Alleles carrying neither **3*, **4*, **5* nor **6* specific mutation, or a duplicated gene were classified as **1*. Alleles carrying a duplicated functional gene are classified as **2 × 2* but could also be **1 × 2*

[a] Could also be **1/*4 × 2*

Genomic DNA was isolated from peripheral leukocytes by Qiagen Blood and Cell Culture DNA kit (Qiagen, Hilden, Germany), according to the guidelines of the manufacturer. The *CYP2D6*3* and *CYP2D6*4* alleles associated with the PM phenotype were determined by allele-specific PCR analysis, as described by Heim and Meyer [30], and the *CYP2D6*6* allele as described by Wennerholm et al. [31]. The *CYP2D6*5* with deletion of the entire *CYP2D6* gene was identified by RFLP assay with the restriction enzyme *Xba*I, as described by Daly et al. [32], and by long-PCR analysis, as described by Wennerholm et al. [31]. All the samples were further analyzed by long-PCR [33] for the duplicated/multiplicated *CYP2D6* gene (designated here as *CYP2D6*2 × 2*). Alleles where neither the defective nor the duplicated genes could be identified were classified as *CYP2D6*1* alleles.

Statistical analysis

The Student's *t*-test for unpaired data was used to compare differences in demographic and clinical characteristics of patients with and without EPS. The chi-square test was used to compare the frequency of the mutated alleles relative to the appearance of EPS. A P value of 0.05 or less was regarded as significant.

Results

The *CYP2D6* genotypes and predicted phenotypes of the patients studied are given in Table 2. In ten patients, a duplicated/multiplicated *CYP2D6* gene was identified, in four cases in association with a *CYP2D6*4* allele. In these four cases, it could not be determined whether the duplicated allele was that with the **4* mutation or the functional *CYP2D6* allele (**1* or **2*). In the other six patients with gene duplication/multiduplication (5% of the population), no mutations were identified and the patients were thus classified as UM.

Homozygous EM, heterozygous EM and UM were equally distributed between the two groups (Table 2), whereas all four PM had a history of EPS. The frequency of detrimental alleles was slightly higher in the group with EPS than in the control group (Table 2), but this difference was not statistically significant ($P > 0.05$). There was no significant difference in the side effects and/or their severity among the different genotypes (Table 3): the AIMS scores (mean ± SD) for tardive dyskinesia among homozygous and among subjects carrying mutated alleles were 5.38 ± 1.92 and 5.71 ± 1.70, respectively, while the SAS scores (mean ± SD) for parkinsonism in the same groups were 4.8 ± 1.9 and 5.1 ± 1.7. No relationship between anticholinergics dose requirement and *CYP2D6* genotype was observed.

Discussion

During the last 20 years, it has been shown that the metabolism of many drugs, including most tricyclic antidepressants and antipsychotics, is catalyzed by the polymorphic CYP2D6 [10, 15]. Individuals heterozygous for defective alleles have on average lower CYP2D6 activity than those homozygous for the functional **1* allele,

Table 3 *CYP2D6* genotype distribution in controls and patients with respect to different types of extrapyramidal side effects (*EPS*)

CYP2D6 Genotypes	**1/*2 × 2*	**1/*1*	**1/*3, *1/*4, *1/*5, *1/*6* or **2 × 2/*4*[a]	**4/*4* or **4/*5*	Total
Controls	3	32	21	0	56
Patients with EPS	3	33	23	4	63
Dystonia	2	9	6	0	17
Parkinsonism	0	13	12	1	26
Tardive dyskinesia	1	3	3	1	8
Dystonia + parkinsonism	0	4	0	1	5
Dystonia + tardive dyskinesia	0	1	0	0	1
Parkinsonism + tardive dyskinesia	0	3	2	1	6
Total	6	65	44	4	119

while subjects homozygous for defective alleles (PM) lack CYP2D6 activity [34, 35]. Furthermore, an allele variant, carrying multiple copies of a functional *CYP2D6* gene (*CYP2D6*1* or *CYP2D6*2*) and associated with extremely high CYP2D6 activity (ultrarapid metabolizers, UM) has been discovered [36, 37]. These findings may explain the large interindividual variability in the plasma concentrations of drugs metabolized by CYP2D6 at fixed dosage schedules and may contribute, at least partially, to differences in therapeutic response. Moreover, different studies [38, 39] suggest that the genetically deficient CYP2D6 metabolic capacity (i.e., the PM status), or the coadministration of inhibitors of this isozyme, may play a significant role in the appearance of adverse reactions to psychotropic drugs.

In the present study on schizophrenic patients genotyped for *CYP2D6*, we found that all four PM subjects had developed EPS. On the other hand, no overrepresentation of one mutated allele, i.e., heterozygous EM, was found among patients with EPS. Nevertheless, the frequency of the detrimental alleles tended to be higher in the EPS group than among controls (24.6% versus 18.7%), although the difference did not reach statistical significance. This is in partial agreement with the hypothesis that carriers of mutated alleles (heterozygous EM and PM) might have an increased risk of developing EPS [27]. Moreover, as in our sample the frequency of UM was similar in the two groups, this status does not seem to play an important role in the occurrence of EPS, though it could lead to lower plasma neuroleptic levels representing, therefore, at least theoretically, a protective condition. However, due to the low number of patients with this genotype, the data are not conclusive.

Our results are similar to previous findings on the role of the *CYP2D6* status in patients with antipsychotic-induced adverse effects. An association between the PM phenotype and acute antipsychotic-induced side effects was reported in a few patients, although the occurrence of acute dystonic reactions did not seem to be related to polymorphic oxidation [23, 24]. In a pilot study [25] of 16 schizophrenic patients with antipsychotic-induced tardive dyskinesia, a relationship was suggested between the degree of impaired CYP2D6 activity and the severity of EPS during antipsychotic treatment, although there was no overrepresentation of PM among the investigated patients. The results of a study carried out in a larger number of patients [26] indicated that the *CYP2D6* genotype is unlikely to be a determinant of susceptibility to acute dystonic reactions, but may be a contributing factor for the occurrence and severity of other antipsychotic-induced movement disorders, including tardive dyskinesia. Similar conclusions were reported in another study [27].

The frequencies of the PM genotype (3.4%) and different *CYP2D6* alleles in the present study are close to those reported earlier in other white Caucasian populations [16, 22, 34, 35, 40] (Table 4). No data are available at the moment on *CYP2D6* allele frequencies in Italian healthy volunteers. In 10 (8.4%) of the patients studied, a duplicated *CYP2D6* gene was identified by *Xba*I RFLP and long-PCR, confirming our previous findings concerning the high frequency of this allele variant in the Italian population [41]. In six of these patients, no detrimental mutations were found, indicating that these subjects have a duplicated functional *CYP2D6* gene (**1* or **2*) and can be expected to have extremely high CYP2D6 activity (UM) [36, 37, 40]. The remaining four patients also carried the *CYP2D6*4* allele, and it cannot be determined whether it is the functional gene or **4* that is duplicated.

Table 4 *CYP2D6* allele frequencies among the patients studied ($n = 119$) and among healthy Caucasian volunteers

	Number of alleles ($n = 238$)	Allele frequency (%)	
		Present study	Healthy Caucasians[a]
CYP2D6*1	176	74	65–70
CYP2D6*3	1	0.4	1–2
CYP2D6*4	41	17.2	20–25
CYP2D6*5	7	2.9	2–4
CYP2D6*6	3	1.3	1–2
CYP2D6*2 × 2	6	2.5	1–3.5
CYP2D6*2 × 2 or *4 × 2	4	1.7	ND

[a] Data from references [16, 34, 35,40]
ND, no data available

In conclusion, although the number of PM in our study is too small to allow generalizations, our findings suggest that the PM condition may contribute to the susceptibility to antipsychotic-induced EPS. Obviously, the dose of the antipsychotic drug(s) plays a major role, but in this retrospective study it was impossible to determine the interaction between dose, plasma antipsychotic level, and genotype in the development of EPS. In this respect, as CYP2D6 is also expressed in the human brain [42], differences in antipsychotic concentration between EM and PM may be even greater in the brain than in plasma. Therefore, knowledge of the *CYP2D6* genotype could allow physicians to give lower initial doses of antipsychotic drugs to the PM and possibly heterozygous EM, thereby reducing the risk of EPS. However, further studies are needed to clarify the clinical value of genotyping patients before starting antipsychotic therapy.

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