Antipsychotic drug-induced movement disorders in schizophrenics in relation to CYP2D6 genotype

MARTIN ARMSTRONG, ANN K. DALY, RICHARD BLENNERHASSETT, NICOL FERRIER and JEFFREY R. IDLE

Background  Approximately 5–10% of Caucasians (poor metabolisers) show impaired metabolism of at least 20 therapeutically important drugs, including a number of commonly used antipsychotic agents, because they lack the cytochrome p450 enzyme CYP2D6. The molecular basis of this defect is now well understood and simple genotyping tests using the polymerase chain reaction (PCR) have been developed.

Method  To determine whether poor metabolisers are more susceptible to acute dystonic reactions and chronic movement disorders associated with the administration of antipsychotic drugs, we determined CYP2D6 genotypes in a group of 76 schizophrenics using previously described methods involving PCR and restriction fragment length polymorphism analysis.

Results  There was no difference in genotype frequencies between the schizophrenics and a normal control population, suggesting that CYP2D6 genotype was not a factor in determining susceptibility to the disease. However, four of the five poor metabolisers compared with 44% of the remaining subjects were suffering from a movement disorder at the time of the study, although because of the small number of poor metabolisers in the group the difference was not statistically significant. Poor metabolisers were not more likely to suffer an acute dystonic reaction.

Conclusions  CYP2D6 genotype is not a determinant of susceptibility to acute dystonic reactions but may be a contributory factor in antipsychotic drug-induced movement disorders including tardive dyskinesia.

Treatment with antipsychotic drugs is associated with a variety of side-effects but one of the most common is the onset of movement disorders, which can include acute dystonic reactions, tardive dyskinesia and Parkinsonian syndrome. Acute dystonic reactions occur in 2–10% of individuals within the first few days of antipsychotic treatment (Grohman et al, 1983). Tardive dyskinesia, akathisia and Parkinsonian syndrome are long-term effects of antipsychotic therapy, and together affect up to 40% of patients (Grohman et al, 1983). It has been suggested that the incidence of movement disorders associated with antipsychotic treatment increases with time on medication (Owens et al, 1982).

The cytochrome p450 enzyme CYP2D6 is the most important enzyme in the oxidative metabolism of the majority of antipsychotic drugs in use today (for review see Cholerton et al, 1992). In most cases, the enzyme catalyses a hydroxylation reaction. However, 5–10% of Caucasians lack this enzyme activity, and those individuals, often referred to as poor metabolisers, have been reported to show high plasma levels of antipsychotic agents (Dahl & Bertilsson, 1993; Jerling et al, 1996). In addition to its role in drug metabolism, CYP2D6 has been detected in human brain and has been suggested to be functionally similar to a dopamine transporter (Niznik et al, 1990). For this reason, the possibility that absence of CYP2D6 activity might influence susceptibility to schizophrenia has been investigated. However, a previous study using in vivo phenotyping found no evidence for an altered incidence of the poor-metaboliser phenotype among schizophrenics (Spina et al, 1992a) and a study of genetic linkage in families with several affected individuals failed to show any association between the CYP2D6 gene and schizophrenia (Vallada et al, 1992). Recently the molecular basis of the CYP2D6 polymorphism has been elucidated, allowing the development of genotyping assays (Heim & Meyer, 1990; Gough et al, 1990; Daly et al, 1991). Genotyping offers a number of advantages; in particular, it eliminates the possibility of interference from other drugs, which is a frequent problem in case–control studies when in vivo phenotyping assays are used. The present study compares the frequency of CYP2D6 genotypes in schizophrenics with a control population, and investigates whether schizophrenics with particular genotypes are more likely to develop antipsychotic-induced movement disorders.

METHOD

Patients  Seventy-six patients (56 male, 20 female, mean age 47 (s.d.=16), all of European Caucasian origin except for one individual of Asian origin), who met the DSM–III–R (American Psychiatric Association, 1987) criteria for schizophrenia were recruited from local hospitals. Informed consent was obtained from each subject and the study was approved by the Newcastle Joint Ethics committee. Subjects were asked to provide a blood sample for genotyping and were assessed for previous dystonic reactions to antipsychotics. The numbers of patients who suffered acute dystonic reactions or a movement disorder are summarised in Table 1. A retrospective study of patient notes was performed to confirm a history of acute dystonia. A clear-cut report of a dystonic reaction was required together with an account of the therapy for the episode and good clinical response to it. The presence of tardive dyskinesia was assessed using the abnormal involuntary movement scale (AIMS; GUY:ECU, 1976). Any subject with a score of four or more was assessed as currently suffering from a movement disorder.

Table 1 Numbers of patients (total n=76) with a history of dystonic reactions and movement disorders

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Acute dystonia</td>
<td>9</td>
<td>67</td>
</tr>
<tr>
<td>Chronic movement disorder (tardive dyskinesia and/or Parkinsonism)</td>
<td>35</td>
<td>41</td>
</tr>
<tr>
<td>Both acute and chronic movement disorders</td>
<td>3</td>
<td>73</td>
</tr>
</tbody>
</table>
disorder. Parkinsonian features were assessed using the Webster Parkinson’s Disease Rating Scale (Webster, 1968), where values of 1-10 indicate early illness. Subjects with a score of three or more were assessed as suffering from a movement disorder. Thirty-five per cent of those suffering from a movement disorder were positive by both the AIMS and Webster scores, 52% by the AIMS only and 13% by Webster alone.

Controls
A control group consisted of 662 healthy volunteers (377 male, 285 female, mean (s.d.) age 35.2 (9.9) years) recruited from the staff of a pharmaceutical company and from the staff and students of the University of Newcastle upon Tyne. All were of European Caucasian origin except for 20 individuals (18 Asian, two Black). The individuals were not specifically screened for mental illness but stated that they did not have any current health problems.

Genotyping
Genomic DNA was isolated from a 10 ml blood sample as described previously (Daly et al, 1991). CYP2D6 genotyping was carried out using the polymerase chain reaction (PCR) and restriction length fragment polymorphism (RFLP) analysis (Daly et al, 1991).

Analysis
Statistical significance was assessed by the χ² test for 2 x k contingency tables (Armitage & Berry, 1987).

RESULTS
Comparison of allele and genotype frequencies in cases and controls
To determine whether schizophrenics showed different allele and genotype frequencies to the normal population, the frequencies of the wild-type (normal allele) and various inactive CYP2D6 alleles (CYP2D6A, CYP2D6B and CYP2D6D) in the schizophrenic group were compared with allele frequencies for the healthy control group. The data are summarised in Table 2. Although there was a slightly increased incidence of the poor metaboliser (homozygous mutant) phenotype among the schizophrenic group, the difference was not significant.

Table 2 CYP2D6 genotype frequencies in schizophrenics (n=76) compared with normal volunteers (n=662)

<table>
<thead>
<tr>
<th></th>
<th>Normal volunteers (95% CI)</th>
<th>Schizophrenics (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Homozygous wild-type</td>
<td>0.55 (0.51–0.59)</td>
<td>0.57 (0.47–0.68)</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>0.40 (0.36–0.44)</td>
<td>0.37 (0.26–0.48)</td>
</tr>
<tr>
<td>Homozygous mutant (poor metabolisers)</td>
<td>0.045 (0.03–0.06)</td>
<td>0.066 (0.01–0.12)</td>
</tr>
</tbody>
</table>

Influence of CYP2D6 genotype on susceptibility to acute dystonic reactions
Nine of the 76 subjects in the study had suffered acute dystonic reactions. Table 5
summarises the CYP2D6 genotype frequencies for these subjects and compares them with frequencies for the remaining subjects. None of the nine subjects was a poor metaboliser and there was no significant difference between the genotype groups with respect to susceptibility to acute dystonic reactions.

**DISCUSSION**

**Allele frequencies in cases and controls**

The present study has confirmed by genotyping techniques previous observations made using metabolic phenotyping that the CYP2D6 polymorphism is not an important factor in determining susceptibility to schizophrenia (Spina et al., 1992a). The frequency of the homozygous mutant (poor metaboliser) genotype in the control group was 4.5%, which is somewhat lower than the value of approximately 8% previously reported for the British population using genotyping assays (Alvan et al., 1990). However, the genotyping methods used have been demonstrated to detect approximately 90% of all phenotypic poor metabolisers in three independent studies (Broly et al., 1991; Dahl et al., 1991; 1992) and the frequency of 4.5% is in good agreement with the value of 4.3% reported by Wolf et al. (1992) in a genotyping study on a group of 720 control subjects from Scotland and Northern England. The frequency of the poor metaboliser phenotype has been demonstrated to show ethnic variation, with frequencies of less than 1% observed among East Orientals (Evan, 1993). However, in the present study the vast majority of both cases and controls were of European Caucasian origin.

**CYP2D6 and susceptibility to acute and chronic movement disorders**

There was no evidence that absence of CYP2D6 activity predisposed towards the development of acute dystonic reactions, which was in agreement with a previous study carried out using phenotyping (Spina et al., 1992b). However, it was found that the majority of patients who lacked CYP2D6 activity were suffering from chronic movement disorders, even though one of them was only 24 years old. This effect failed to reach statistical significance because of the relatively small number of poor metabolisers in the present study. There was also a trend towards an increased risk of movement disorder in individuals with at least one mutant CYP2D6 allele present, suggesting that heterozygotes also carry an increased risk. These findings are in general agreement with the conclusions of a recent study on a small group of patients with tardive dyskinesia, which found that there was a relationship between degree of impairment of CYP2D6 activity and severity of the movement disorder (Arthur et al., 1995).

**Significance and possible basis of the apparent association**

Movement disorders develop in a high percentage of those taking antipsychotic drugs (Grohman et al., 1983) and since absence of CYP2D6 activity occurs in only approximately 5% of the population, it is unlikely that absence of this enzyme activity is the major cause of these disorders. However, knowledge of CYP2D6 genotype could enable a lower dose of the antipsychotic drug to be administered to poor metabolisers and might reduce the risk of the onset of the movement disorder, particularly in younger patients.

Pharmacokinetic studies have shown marked differences between poor and extensive metabolisers with respect to clearance of several antipsychotics including perphenazine, zuclopenthixol, thioridazine and haloperidol (Dahl-Puustinen et al., 1989; von Bahr et al., 1991; Llerena et al., 1992; Jerling et al., 1996). In the present study, poor metabolisers had a three- to four-fold higher serum concentration of the drug than extensive metabolisers, and a 10-fold higher concentration 24 hours after drug intake (Dahl-Puustinen et al., 1989). Perphenazine normally undergoes considerable first-pass metabolism and this accentuates pharmacokinetic differences between poor and extensive metabolisers.

**CONCLUSIONS**

In conclusion, it is clear that CYP2D6 genotype is not the major factor that determines susceptibility to antipsychotic-induced movement disorders. It may, however, be a contributory factor and consideration of genotype may be useful in reducing the incidence of these serious adverse reactions and their severity in susceptible subjects.

**REFERENCES**


**Table 5** Acute dystonia in the schizophrenia group

<table>
<thead>
<tr>
<th></th>
<th>Homozygous wild-type</th>
<th>Heterozygous</th>
<th>Homozygous mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute dystonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=9)</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>No (n=67)</td>
<td>39</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Frequency</td>
<td>0.09</td>
<td>0.18</td>
<td>0</td>
</tr>
</tbody>
</table>

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The CYP2D6 genotype predicts the oral clearance of the neuroleptic agents perphenazine and zulcopenthixol. Clinical Pharmacology and Therapeutics, 59, 423–428.


**CLINICAL IMPLICATIONS**

- CYP2D6 genotype is not a factor in susceptibility to schizophrenia.
- CYP2D6 genotype does not determine susceptibility to acute dystonic reactions.
- CYP2D6 genotype may be a factor in determining susceptibility to antipsychotic drug-induced movement disorders including tardive dyskinesia.

**LIMITATIONS**

- Although a trend in the relationship between CYP2D6 genotype and susceptibility to chronic movement disorders was observed, the difference was not statistically significant.
- The study involved only a small number of schizophrenics and a larger study is required to confirm the findings.
- There were insufficient patients in the study suffering from either tardive dyskinesia alone or Parkinsonism alone to allow the relationship between CYP2D6 genotype and either condition alone to be investigated.
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References
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