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Clomipramine, fluoxetine and CYP2D6 metabolic capacity in depressed patients

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Cytochrome P450-2D6 may be involved in the metabolism of many drugs such as psychotropic drugs and its genetic polymorphism is responsible for inter-individual differences in the therapeutic effect and toxicity of these drugs. Moreover with the same genetic basis, CYP2D6 metabolic capacity variations are observed. Different factors of variation may be involved, among them the prescribed drugs.

The aim of this study was to compare the influence of two types of antidepressants, tricyclic (clomipramine) and serotonergic specific recapture inhibitor (SSRI) (fluoxetine), on the CYP2D6 metabolic capacity of depressed inpatients. The CYP2D6 phenotype (dextromethorphan test) was determined in 56 genotyped (PCR-SSCP) depressed caucasian inpatients with a heterozygous genotype. Forty-five subjects were treated with clomipramine and eleven received fluoxetine. The dextromethorphan metabolic ratio (MR) median was significantly higher in the fluoxetine group (0.255) than in the clomipramine group (0.083, $p < 0.014$). In this study, fluoxetine involved a greater decrease of CYP2D6 metabolic capacity than clomipramine. Clinical implications and the possible connection between a decreased CYP2D6 activity and adverse drug effects were discussed. Caution should be taken when drugs with a low therapeutic index must be coprescribed in such patients. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — CYP2D6; phenotype; clomipramine; fluoxetine

INTRODUCTION

Cytochrome P450-2D6 (CYP2D6) is involved in the metabolism of many psychotropic drugs, among them specific serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) that are widely prescribed (Baumann, 1986; Bertilsson and Dahl, 1996; Brosen and Gram, 1989; Cholerton *et al.*, 1992; Eichelbaum and Gross, 1990; Tanaka, 1998). Its genetic polymorphism is responsible for inter-individual differences in the therapeutic effect and toxicity of many drugs (Brosen and Gram, 1989; Chen *et al.*, 1996; Spina *et al.*, 1992; Spina *et al.*, 1994; Vandel *et al.*, 1999). Moreover with the same genetic basis, intra-individual CYP2D6 metabolic capacity variations are observed in patients, with possible clinical implications. Different factors of variation may be involved, drug treatment being an important one.

Patients receiving CYP2D6 substrate medications are likely to experience a temporary decrease of their CYP2D6 metabolic capacity. The CYP2D6 affinity varies among psychotropic drugs. Fluoxetine, a SSRI antidepressant, is characterized *in vitro* by a CYP2D6 affinity higher than clomipramine, a tricyclic antidepressant, for example (Crewe *et al.*, 1992; Nielsen *et al.*, 1996; Ball *et al.*, 1997). Fluoxetine and its active metabolite norfluoxetine are considered as strong inhibitors of CYP2D6 metabolic capacity (Brosen and Skjelbo, 1991; Crewe *et al.*, 1992). Among the tricyclic antidepressants, clomipramine may also diminish the CYP2D6 activity to a lesser extent (Crewe *et al.*, 1992).

The consequence of these affinities for the CYP2D6 isoenzyme is that coprescription of these drugs may

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reduce the clearance of all drugs metabolized by this isoform of CYP450. But it is difficult to extrapolate from *in vitro* data to the *in vivo* potentiality of metabolic modification. A difference in the inhibition potential of the drugs may lead to different variations in the CYP2D6 metabolic capacity, and possible consequences on differing drug bioavailability.

The aim of the present work was to compare and quantify *in vivo* the influence of clomipramine and fluoxetine on the CYP2D6 metabolic capacity of depressed inpatients and to see if some clinical implications may be induced.

METHODS

Patients

Fifty-six CYP2D6 genotyped caucasian inpatients suffering from depressive illness (major depression and dysthymic disorders, DSM IV—R criteria: 23 men and 33 women; age range 18–75 years; mean $43.5 \pm$ SD 18.8) were included in the study. The main characteristics are presented in Tables 1 and 2.

Forty-five subjects were treated with the tricyclic antidepressant clomipramine, and 11 with a SSRI antidepressant fluoxetine, both drugs with CYP2D6 affinity (Bertilsson and Dahl, 1996; Brosen, 1993; Otton *et al.*, 1993). The dosage of oral clomipramine varied between 100 and 150 mg/day (mean $116.66 \pm$ SD 20.1). The dosage of fluoxetine was 20 mg/day for all the patients. Most of the patients received comedication with a benzodiazepine at the usual dosage, drugs with no known affinity for CYP2D6 (Anderson *et al.*, 1994) and with no other drug known to affect this CYP metabolism (Tables 1, 2).

The duration of the clomipramine treatment was 3 weeks or more and more than 4 weeks for the fluoxetine treatment.

Patients were free of kidney and liver disease and without elevation of liver enzymes when entering the study and at 1 month after beginning the treatment.

Clinical monitoring

As usual in our psychiatric ward, the side effects were recorded (without scale) every day during the daily clinical round of inspection.

CYP2D6 phenotyping procedure

The determination of the patient's CYP2D6 metabolic activity was made at the end of 3 weeks for clomipramine treatment and at the end of 4 weeks for fluoxetine, by using a phenotyping test (HPLC determination of urinary dextromethorphan and its metabolite dextrorphan in 8 h urine sample after a single oral dose of 25 mg dextromethorphan) (Küpfer *et al.*, 1984) in a steady state condition of antidepressant treatment. The usual classification of extensive (EM) and poor (PM) metabolizers was made according to the metabolic ratio in the 8 h urine sample (Schmid *et al.*, 1985): EM, dextromethorphan/dextrorphan <0.3; PM, dextromethorphan/dextrorphan >0.3.

CYP2D6 genotype determination

The CYP2D6 genotype was determined before the beginning of the treatment, using single-strand conformation polymorphism analysis (SSCP) of the gene amplified by polymerase chain reaction (PCR) analysis by Broly *et al.* (1995).

Statistical analysis

The normality test (Kolmogorov–Smirnov) was used to test the normality of the distribution of MR results. Nonparametric stastistical methods (Mann–Whitney) were performed to compare the two phenotype group values.

RESULTS

Genotyping data

In the 56 patients studied, there was no patient with an homozygous genotype (*1/*1), all were characterized by an heterozygous genotype. Twenty-five were carriers of a CYP2D6*1/CYP2D6*2 and 31 patients had a CYP2D6*1/CYP2D6*4 heterozygous genotype.

Phenotyping data

The dextromethorphan metabolic ratio ranged from 0.003 to 2.68 (median 0.088) in the whole population and 16 patients were classified as PM (28.57%). It ranged from 0.003 to 1.324 in the group of patients treated with clomipramine, whereas it was from 0.028 to 2.68 in the group of patients receiving fluoxetine. Eleven patients were classified as PM in the clomipramine group (24.4%) and five as PM in the fluoxetine group (45.5%).

The normality test failed (K-s dist $= 0.000$; $p < 0.001$) indicating that the MR distribution was not normal.

Table 1. Characteristics of genotyped and phenotyped patients treated with clomipramine

Patient	Sex	Age	Antidepressant treatment (mg/d)	Comedication (mg/d)	Genotype	Allelic metabolic capacity	Metabolic ratio	Metabolic capacity	Drug side effect
1	M	19	Clomipramine 100	Prazepam 20	*1A/*2	EM/IM	0.077		
2	F	65	Clomipramine 100	Prazepam 20	*1A/*2	EM/IM	0.019		
3	M	39	Clomipramine 100	Bromazepam 6	*1A/*2	EM/IM	0.015		
4	F	75	Clomipramine 150	Alprazolam 0.5	*1A/*2	EM/IM	0.123		Yes
5	F	65	Clomipramine 100		*1A/*2	EM/IM	0.13		Yes
6	F	23	Clomipramine 112.5	Prazepam 20	*1A/*2	EM/IM	0.003		
7	M	30	Clomipramine 112.5	Alprazolam 0.5	*1A/*2	EM/IM	0.01		
8	M	44	Clomipramine 112.5	Prazepam 20	*1A/*2	EM/IM	0.028		
9	F	32	Clomipramine 100	Oxazepam 10	*1A/*2	EM/IM	0.054		Yes
10	F	66	Clomipramine 137.5	Clorazepate 75	*1A/*2	EM/IM	0.029		
11	F	72	Clomipramine 125	Bromazepam 6	*1A/*2	EM/IM	0.091		Yes
12	F	18	Clomipramine 100	Prazepam 20	*1A/*2	EM/IM	0.284		Yes
13	F	34	Clomipramine 100	Prazepam 20	*1A/*2	EM/IM	0.003		
14	F	43	Clomipramine 100	Bromazepam 6	*1A/*2	EM/IM	0.083		
15	F	37	Clomipramine 150	Alprazolam 0.5	*1A/*2	EM/IM	0.185		
16	F	22	Clomipramine 100	Prazepam 20	*1A/*2	EM/IM	1.125	PM	Yes
17	M	28	Clomipramine 100	Prazepam 20	*1A/*2	EM/IM	0.01		
18	M	20	Clomipramine 150	Prazepam 20	*1A/*2	EM/IM	0.436	PM	
19	F	25	Clomipramine 100		*1A/*2	EM/IM	0.012		
20	M	67	Clomipramine 100	Alprazolam 1.5	*1A/*2	EM/IM	0.08		
21	M	55	Clomipramine 137.5	Clorazepate 75	*1A/*4A	EM/PM	0.017		
22	F	69	Clomipramine 150	Prazepam 20	*1A/*4A	EM/PM	0.379	PM	Yes
23	M	71	Clomipramine 112.5	Prazepam 20	*1A/*4A	EM/PM	0.075		
24	M	30	Clomipramine 100	Prazepam 20	*1A/*4A	EM/PM	0.009		
25	F	72	Clomipramine 100	Alprazolam 1.5	*1A/*4A	EM/PM	0.06		Yes
26	F	23	Clomipramine 100	Prazepam 20	*1A/*4A	EM/PM	0.099		Yes
27	M	67	Clomipramine 112.5	Oxazepam 10	*1A/*4A	EM/PM	0.012		Yes
28	F	28	Clomipramine 100	Clorazepate 75	*1A/*4A	EM/PM	0.06		Yes
29	M	23	Clomipramine 100	Prazepam 20	*1A/*4A	EM/PM	0.017		Yes
30	M	50	Clomipramine 150	Prazepam 20	*1A/*4A	EM/PM	0.299		Yes
31	F	67	Clomipramine 112.5	Alprazolam 0.5	*1A/*4A	EM/PM	0.264		
32	F	41	Clomipramine 150	Prazepam 20	*1A/*4A	EM/PM	0.872	PM	
33	M	22	Clomipramine 150	Bromazepam 6	*1A/*4A	EM/PM	0.880	PM	Yes
34	F	30	Clomipramine 137.5		*1A/*4A	EM/PM	0.950	PM	Yes
35	M	50	Clomipramine 100	Alprazolam 2	*1A/*4A	EM/PM	0.101		
36	F	20	Clomipramine 100	Prazepam 20	*1A/*4A	EM/PM	0.093		Yes
37	M	72	Clomipramine 137.5	Oxazepam 10	*1A/*4A	EM/PM	0.017		
38	F	28	Clomipramine 137.5	Clorazepate 75	*1A/*4A	EM/PM	0.999	PM	Yes
39	M	21	Clomipramine 100	Prazepam 20	*1A/*4A	EM/PM	0.009		Yes
40	M	51	Clomipramine 112.5	Bromazepam 6	*1A/*4A	EM/PM	0.304	PM	
41	F	67	Clomipramine 150	Prazepam 20	*1A/*4A	EM/PM	1.058	PM	Yes
42	F	31	Clomipramine 112.5	Prazepam 20	*1A/*4A	EM/PM	0.309	PM	
43	F	66	Clomipramine 137.5		*1A/*4A	EM/PM	0.181		Yes
44	F	46	Clomipramine 100	Alprazolam 0.5	*1A/*4A	EM/PM	0.037		
45	M	23	Clomipramine 100	Bromazepam 6	*1A/*4A	EM/PM	1.324	PM	

MR, metabolic ratio; EM, extensive metabolism; IM, intermediate metabolism; PM, poor metabolizer.

Antidepressant effects on phenotype

For the first time, the phenotypes of the two groups of patients treated with the two different antidepressants were compared to try to determine if the metabolic capacity modification induced by these two types of antidepressants differed.

Tables 1 and 2 present the influence of the two antidepressants on the expression of the CYP2D6 gene. A significant difference was observed. In the clomipramine group, the median metabolic ratio was 0.083, and 0.255 in the fluoxetine group ($p < 0.0145$).

Antidepressant side effects

Between the weeks 2 and 4 of treatment, side effects appeared in 26 patients.

In the group of patients receiving fluoxetine, six (54%) suffered from very light extrapyramidal effects such as tremor, inducing no treatment modification.

Table 2. Characteristics of genotyped and phenotyped patients treated with fluoxetine

Patient	Sex	Age	Antidepressant treatment (mg/d)	Comedication (mg/d)	Genotype	Allelic metabolic capacity	Metabolic ratio	Metabolic capacity	Drug side effect
1	M	44	Fluoxetine 20	Prazepam 20	*1A/*2	EM/IM	0.028		
2	F	43	Fluoxetine 20		*1A/*2	EM/IM	0.083		
3	F	34	Fluoxetine 20	Alprazolam 2	*1A/*2	EM/IM	0.082		
4	F	22	Fluoxetine 20		*1A/*2	EM/IM	1.215	PM	Yes
5	F	26	Fluoxetine 20		*1A/*2	EM/IM	1.114	PM	Yes
6	F	51	Fluoxetine 20		*1A/*4A	EM/PM	0.122		
7	F	53	Fluoxetine 20	Prazepam 20	*1A/*4A	EM/PM	2.68	PM	Yes
8	F	74	Fluoxetine 20		*1A/*4A	EM/PM	0.078		Yes
9	M	67	Fluoxetine 20		*1A/*4A	EM/PM	0.255		Yes
10	M	30	Fluoxetine 20	Oxazepam 10	*1A/*4A	EM/PM	0.647	PM	
11	M	45	Fluoxetine 20	Prazepam 20	*1A/*4A	EM/PM	1.191	PM	Yes

MR, metabolic ratio; EM, extensive metabolism; IM, intermediate metabolism; PM, poor metabolizer.

Twenty patients (44%) treated with clomipramine suffered from one or more adverse effects such as orthostatic hypotension ($n = 12$), dry mouth ($n = 15$), constipation ($n = 8$), accommodation disturbance ($n = 8$) or tremor ($n = 3$). In three cases (hypotension) clomipramine was stopped and citalopram (two cases) or venlafaxine (one case) was prescribed. In 17 cases a corrective treatment or a modification of the clomipramine dosage ($n = 10$) led to an improvement of the drug tolerance. There was the opportunity to perform a second CYP2D6 phenotype in five patients, 1 week after the decrease in clomipramine dosage and tolerance improvement. A decrease of the MR was observed (MR values before and after the treatment decrease: 0.284 to 0.234; 0.379 to 0.297; 0.299 to 0.254; 0.880 to 0.807; 0.181 to 0.132). No other serious side effect of the tricyclic antidepressant was observed.

When considering the existence of drug side effects, two groups of patients must be compared. The MR difference between these groups was statistically significant (median 0.181 in the group with side effects and 0.075 in the other one; $p < 0.0022$).

DISCUSSION

Genotyping data

The 56 patients were characterized by an heterozygous genotype. Among CYP2D6 genotypes, heterozygous genotypes characterized by the association of a wild allele *1 with a mutant allele, are the most frequent and induce a partially impaired debrisoquine hydroxylation (Daly *et al.*, 1991; Daly *et al.*, 1996). All our patients were considered heterozygous EMs (or IMs) because of the presence of CYP2D6*1 in their gene, but their metabolic potentiality was lower than that of homozygous EMs.

Phenotyping data

As expected, the number of PM phenotypes in our population of depressed patients treated with substrates and inhibitors of CYP2D6 was high (28.5%). In the general untreated population, about 7% to 10% of caucasians are poor metabolizers of sparteine (or dextromethorphan) showing impaired oxidation of this drug and those using CYP2D6 for their biotransformation, due to defective forms of the gene encoding the enzyme CYP2D6 (Gonzalez *et al.*, 1988).

This result is in agreement with those of our previous studies (Derenne *et al.*, 1989; Perault *et al.*, 1991; Vandel *et al.*, 1999). It was probably due to the saturation of the metabolic pathways by the antidepressants. CYP2D6 is involved in the metabolism of tricyclic antidepressants and SSRIs (Baumann, 1986; Bertilsson and Dahl, 1996; Brosen and Gram, 1989; Cholerton *et al.*, 1992; Eichelbaum and Gross, 1990; Tanaka, 1998). The intensity of the modification of CYP2D6 expression may vary depending mainly on the CYP2D6 affinity of the prescribed drug, and on its dosage.

Difference in the antidepressant effect on phenotypes?

Two different antidepressants were prescribed, clomipramine and fluoxetine, both substrates and/or inhibitors of CYP2D6. So the two patient groups may be compared.

The median metabolic ratio was higher in the group of patients with fluoxetine than in the other group receiving clomipramine (0.255 versus 0.083 respectively; $p < 0.0145$).

An influence of comedication may not to be considered since the patients of the two groups received antidepressant alone or comedication with benzodiazepines. These latter drugs are not substrates or inhibitors of CYP2D6 (Anderson *et al.*, 1994).

The role of age may be eliminated due to the fact that the means of the patient age were not different between these groups (clomipramine group: 43.2 ± 19.5 and fluoxetine group: 44.4 ± 16.3).

The only remaining qualitative difference was the antidepressant treatment with SSRI or tricyclic antidepressants. Our results, however, should be considered with caution due to the fact that CYP2D6 inhibition may be related in part to dose and plasma concentration (Alfaro *et al.*, 2000). However, the stronger inhibiting effect of fluoxetine might be a result of the 1 week longer duration of this SSRI than of clomipramine treatment. But the full CYP2D6 inhibition may be contemporaneous with the steady state of the drug plasma level and the delay of fluoxetine is longer than clomipramine.

The *in vivo* data tended towards the *in vitro* notion of a quantitative difference of CYP2D6 affinities between the two antidepressants. The data are also in agreement with those of drug interaction studies between these antidepressants. A tenfold increase in tricyclic plasma concentrations was seen when fluoxetine was coadministered (Bergström *et al.*, 1992; Vandel *et al.*, 1992) showing that tricyclic antidepressants possess a lower CYP2D6 affinity than fluoxetine.

Clinical implications?

The question is whether the decrease of CYP2D6 metabolic capacity has a clinical implication? Clinical reports showed that patients who were carriers of the heterozygous genotype may suffer more frequently from drug side effects (Chen *et al.*, 1996; Spina *et al.*, 1997) and that drug overdosage and side effects appeared more frequently in patients with a decreased metabolic capacity (Brosen and Gram, 1989; Chen *et al.*, 1996; Arthur *et al.*, 1995; Leon *et al.*, 1998; Spina *et al.*, 1997).

In our study, all patients were carriers of an heterozygous genotype. Heterozygous genotypes (with a wild allele) are characterized by a partially impaired debrisoquine hydroxylation capacity (Daly *et al.*, 1991; Daly *et al.*, 1996) and antidepressant treatment may worsen this deficiency. In our population, the MR difference between the group of patients suffering from drug side effects and the group of patients with a good drug tolerance was statistically significant (median 0.181 in the group with side effects and 0.075 in the other; $p < 0.0022$). But the results of a recent study, (Roberts *et al.*, 2004) suggested that the CYP2D6 metabolic inefficiency did not necessarily lead to an increased occurrence of antidepressant (fluoxetine or nortriptyline) side effects in monotherapy conditions. In our study, all patients with the PM phenotype did not suffer from side effects. It is possible that in the Robert's population some patients genotyped as EM became phenotyped as PM even with monotherapy. These results are not really in discrepancy.

Moreover the difference in data found in the literature may be due to problems of methodology. It is quite impossible to select an homogeneous population for all factors other than those studied. For example, it is not possible to evaluate the receptor sensibility that also plays a major role in the drug response.

The notion concerning the therapeutic difference of drug enantiomers compared with the racemate (Hindmarch, 2001) may be another explanation of the data differences. Each enantiomer of a chiral antidepressant may be characterized by individual pharmacological, pharmacokinetic and pharmacogenetic profile, and may be metabolized by different enzymes. Fluoxetine is a chiral antidepressant (Baumann and Eap, 2001). It would be interesting to introduce a determination of enantiomers in future studies.

Our results suggest an *in vivo* higher inhibition of CYP2D6 metabolic capacity by fluoxetine than clomipramine in a population of heterozygous genotyped patients.The knowledge of the genotype might be useful in a large population, both in the prediction and prevention of drug side effects and in the choice of drugs or comedications with a lower CYP2D6 affinity in patients with a previous high loss of CYP2D6 activity. Caution must be taken especially when CYP2D6 substrate drugs with a low therapeutic index have to be coprescribed in patients characterized by an heterozygous genotype.

The experiments comply with the current French laws. Informed consent was obtained from all subjects and the methods were approved by the 'Comité de Protection des Personnes soumises à la Recherche Biomédicale' at Besançon Universitary Hospital.

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