# Pharmacogenetic Study of the Response to Flecainide and Propafenone in Patients With Atrial Fibrillation

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We analyzed cytochrome P450 2D6 polymorphism by determining phenotype as the metabolic ratio between dextromethorphan and its main metabolite, dextrorphan. We studied 18 men and 22 women in whom mean age was 54.6±11.9 years. In 9 patients metabolic ratio was determined before antiarrhythmic treatment and again during treatment, with a mean increase of 0.13±0.15 (*P*=.03). We found 19 poor metabolizers and 21 extensive metabolizers. Adverse effects were more frequent in poor metabolizers (21.1%) than in extensive metabolizers (4.8%; *P*=.12). Antiarrhythmic treatment was effective in 27 patients (67.5%), with no difference between poor and extensive metabolizers.

**Key words:** *Atrial fibrillation. Genetics. Pharmacogenetics. Polymorphism. Cytochrome P450 2D6.*

**Estudio farmacogenético de la respuesta a flecainida y propafenona en pacientes con fibrilación auricular**

Se analizó el polimorfismo del citocromo P450-2D6 mediante la determinación del fenotipo, utilizando la ratio entre dextrometorfano y su metabolito dextrorfano. Estudiamos a 18 varones y 22 mujeres, con una edad media de 54,6 ± 11,9 años. En 9 pacientes se realizó una determinación de la ratio metabólica antes de iniciar el tratamiento antiarrítmico y una segunda determinación bajo tratamiento, con un incremento promedio de 0,13 ± 0,15 (p = 0,03). De los 40 pacientes, 19 eran metabolizadores lentos y 21 metabolizadores rápidos. Los efectos secundarios fueron más frecuentes en los metabolizadores lentos (21,1%) que en los metabolizadores rápidos (4,8%) (p = 0,12). El tratamiento antiarrítmico fue eficaz en 27 pacientes (67,5%), con un porcentaje similar en metabolizadores lentos y rápidos.

**Palabras clave:** *Fibrilación auricular. Genética. Farmacogenética. Polimorfismo. CYP2D6.*

## INTRODUCTION

Flecainide and propafenone are effective agents for reversion or prevention of atrial fibrillation (AF). Nevertheless, both drugs have arrhythmogenic potential and it is difficult to predict whether the antiarrhythmic or the proarrhythmic effect will prevail.[1] Furthermore, the incidence of adverse effects is high.[2] CYP2D6 is responsible for propafenone and flecainide metabolism, with a between-individual variation of up to 10 000-fold observed in its metabolic activity[3] and 2 clearly differentiated phenotypes: poor metabolizers (PM) and extensive metabolizers (EM).[4] Scientific evidence also indicates the existence of a third population, the ultra extensive metabolizers (UEM).[5,6]

Our objective was to study the interrelationships of the phenotypic variants of the *CYP2D6* gene with propafenone or flecainide therapy.

## PATIENTS AND METHODS

The study retrospectively included patients with AF who, after electrical, pharmacological or spontaneous cardioversion, received propafenone or flecainide between January 1999 and October 2002, and also pros-

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ABBREVIATIONS

CYP2D6: cytochrome P450 2D6 isoenzyme.
AF: atrial fibrillation.
PM: poor metabolizers.
EM: extensive (standard) metabolizers.
UEM: ultra extensive metabolizers.
MR: metabolic rate.

pectively included patients from November 2002. The cardiologists who performed the dose titration were blinded to the phenotyping results. The following were recorded: *a)* efficacy: <1 recurrence (onset of symptoms clearly suggestive of tachyarrhythmia and/or electrocardiographic evidence of AF) every 2 months and lasting <1 h, and *b)* adverse effects that led to discontinuation of therapy or lower dosage, recorded only the first time they appeared.

Patients with any of the following criteria were excluded: *a)* structural heart disease; *b)* liver, renal, or other disease that significantly shortened life expectancy or affected drug excretion; *c)* age younger than 18; *d)* pregnancy; *e)* poor compliance with therapy (more than one noncompliance per week); and *f)* failure to give written informed consent.

CYP2D6 polymorphism was determined by measuring its enzyme activity, using the ratio of dextromethorphan to dextrorphan metabolite in urine, 8 h after the administration of 30 mg of dextromethorphan (metabolic rate, MR).[4,5] The patients were classified into 3 phenotype groups, according to MR: *a)* PM >0.3[4]; *b)* UEM<0.005 as the most commonly accepted threshold[5,6]; and *c)* EM 0.3-0.005. The MR was determined after antiarrhythmic therapy was started, although in 9 patients it was obtained before and after therapy. Patients were classified using the post-therapy determination.

The investigator analyzing the data and classifying patients according to clinical response was blinded to the phenotype data. To assess the independent effect of CYP2D6 metabolism on adverse effects or therapeutic efficacy, logistic regression analyses were performed in which potential confounding variables were controlled. SPSS 11.0 was used for the statistical analysis.

## RESULTS

Among the 40 patients, 27 (67.5%) were on flecainide, 6 (15.0%) on propafenone, and 7 (17.5%) on both drugs in different periods. The median time from the start of antiarrhythmic therapy until the MR determination was 21 months, and the mean clinical follow-up from the start of treatment was 3.4 years (range, 6 months to 6.1 years). No patient was lost to follow-up.

The MR of the 40 patients during antiarrhythmic therapy was between 0.008 and 7.3, with a mean of 0.5±1.3. An MR was also obtained in 9 patients before therapy, with an increase of 0.13±0.15 (*P*=.03) observed after therapy; 4 patients (44.4%) went from EM to PM, while the remaining 5 showed no change in phenotypic group.

In terms of phenotype obtained under therapy, 19 patients were PM and 21, EM. The clinical profiles are shown in Tables 1 and 2. Five patients presented adverse effects in the first 6 months (21.1% among PM vs 4.8% in EM; *P*=.091). Only the PM presented adverse effects that led to discontinuation of therapy (Table 3). The multivariate analysis, when controlling for

TABLE 1. **Clinical Characteristics, Previous Procedures, Concomitant Antiarrhythmic Medication, and Tobacco/Alcohol Use According to CYP2D6 Phenotype***

| | Poor Metabolizers, n=19 (%) | Extensive Metabolizers, n=21 (%) |
|---|---|---|
| Age, years, mean ± SD | 57.1±10.4 | 52.3±12.8 |
| Male sex, n (%) | 7 (36.8) | 11 (52.4) |
| Weight, kg, mean ± SD | 72.2±10.1 | 76.6±18.6 |
| Previous procedures, n (%) | | |
| Electrical cardioversion | 3 (15.8) | 3 (14.3) |
| Ablation of pulmonary veins | 4 (21.1) | 3 (14.3) |
| Unsuccessful pulmonary vein ablation | 1 (5.3) | 1 (4.8) |
| Ablation of cavotricuspid isthmus | 1 (5.3) | 3 (14.4) |
| Coffee intake, n (%) | 9 (50.0) | 6 (28.6) |
| Active smoker, n (%) | 4 (21.1) | 5 (19.1) |
| Antiarrhythmic therapy, n (%) | | |
| Digoxin | 0 (0.0) | 1 (4.8) |
| Beta-blockers | 4 (21.1) | 3 (14.3) |
| Amiodarone | 0 (0.0) | 3 (14.3) |
| Calcium antagonists | 2 (10.5) | 1 (4.8) |

*SD indicates standard deviation

TABLE 2. **Other Concomitant Medication According to CYP2D6 Phenotype***

| | Poor Metabolizers, n=19 (%) | Extensive Metabolizers, n=21 (%) |
|---|---|---|
| Anticoagulation | 12 (63.2) | 10 (47.6) |
| Antiplatelet agents | 4 (21.1) | 7 (33.3) |
| ACE inhibitors | 4 (21.1) | 4 (19.0) |
| Statins | 4 (21.1) | 3 (14.3) |
| Gastroprotective agents | 3 (15.8) | 4 (19.0) |
| Diuretics | 4 (21.1) | 3 (14.3) |

*ACE inhibitors indicates angiotensin-converting enzyme inhibitors.

variables that could influence the onset of adverse effects (age, sex, tobacco/alcohol use, and concomitant antiarrhythmic therapy introduced as a dichotomous variable) showed an odds ratio (OR) of 2.9 (95% confidence interval [CI], 0.3-26.3) for PM versus EM.

Antiarrhythmic therapy was effective in 27 patients (67.5%), with a similar percentage in both the PM (63.2%) and the EM (71.4%) (*P*=.74). The multivariate analysis showed no independent effect of metabolism type on therapeutic efficacy (OR for PM=0.7; 95% CI, 0.2-2.6). We also found no differences in the mean dose of flecainide (PM, 214±54; EM, 210±74; *P*=.87) or propafenone (600±193 vs 510±251, respectively; *P*=.52).

## DISCUSSION

Almost half the patients in our study were PM, a surprising finding when compared to previous studies conducted among healthy volunteers, which reported a PM prevalence of 5%-10% among the white population.[7] In addition, we observed no UEM in our sample. The prevalence of UEM among the white population and, in particular, among healthy volunteers in Spain is estimated at 7%.[6] Therefore, among healthy volunteers the remaining 82%-85% would be EM, whereas in our sample only 21 of the 40 patients were EM. One of the most important findings of our study was that propafenone or flecainide therapy increased the average MR. In addition, in 4 out of 9 patients this led to a change from EM to PM, supporting the findings of Haefeli et al,[8] who observed CYP2D6 inhibition produced by flecainide among healthy volunteers. This inhibition, in combination with the frequent administration of concomitant medication, could explain the high prevalence of PM observed and the absence of UEM.

The fact that flecainide and propafenone therapy increased MR, and therefore reduced CYP2D6 activity, could have contributed to the high incidence of adverse effects seen in our study and previous studies.[2] In our sample, these effects were more frequent in PM, although the difference was not statistically significant. To our knowledge, no earlier series have analyzed the incidence of adverse effects according to the phenotype profile of CYP2D6, although 1 case of serious adverse effects was described in a patient treated with propafenone, associated with low CYP2D6 metabolism.[9]

We have not, however, been able to demonstrate any phenotype-related differences in the efficacy of the drugs. Jazwinska-Tarnawska et al[10] studied a similar number of patients on propafenone, finding a correlation between phenotype and the persistence of sinus rhythm. This might be because these authors' series did have UEM, who, moreover, presented an efficacy of 0%. Our sample was small, very heterogeneous, and had undergone a number of previous procedures. Even if we assume that phenotype influences flecainide or propafenone efficacy, many other factors also influence the effect of treatment. Because the sample was limited, the statistical power was insufficient to detect a possible effect of phenotype on treatment efficacy.

Some of our patients were included prospectively and others retrospectively, which could imply a classification bias, and follow-up times were variable. The possibility of bias was minimized since the cardiologists were not aware of the phenotyping results. In addition, we were unable to determine blood concentrations and therefore are unaware of any correlation with the CYP2D6 phenotype.

Despite its limitations, our study shows that treatment with flecainide and propafenone reduces the activity of the isoenzyme responsible for their metabolization. Although we do not know the implications of this reduced activity, poor CYP2D6 metabolism

TABLE 3. **Patients Who Presented Adverse Effects in the First 6 Months of Flecainide or Propafenone Therapy, According to CYP2D6 Phenotype***

| | PM, n (%) | EM, n (%) | Type of Adverse Effect With Flecainide | Type of Adverse Effect With Propafenone |
|---|---|---|---|---|
| Adverse effects leading to discontinuation of therapy | 4 (21.1) | 0 | Insomnia/restlessness<br>Constipation | General discomfort<br>Transaminase elevation |
| Adverse effects with both drugs | 1 (5.3) | 0 | Bitter taste | Transaminase elevation |
| Adverse effects leading to dose reduction | 0 | 1 (4.8) | Bitter taste | Sinus bradycardia |

*PM indicates poor metabolizers; EM, extensive metabolizers.

experienced after therapy may produce a higher incidence of adverse effects. Additional pharmacogenetic studies under routine clinical conditions are needed to assess the impact of genetic polymorphisms and to elucidate the role of genotype and phenotype in antiarrhythmic dose titration and reduction of adverse effects.

## REFERENCES


1. Cosío FG, Delpón E. New antiarrhytmic drugs for atrial flutter and atrial fibrillation. Circulation. 2002;105:276-8.
2. Feld GK, Chen P-S, Nicod P, Fleck P, Meyer D. Possible atrial proarrhythmic effects of class 1C antiarrhythmic drugs. Am J Cardiol. 1990;66:378-83.
3. McElroy S, Richmond J, Lira M, Fiedman D, Silber BM, Milos PM. *CYP2D6* genotiping as an alternative to phenotyping for determination of metabolic status in a clinical trial setting. AAPS Pharmsci. 2000;2:1-13.
4. Henthorn TK, Benítez J, Avram MJ, Martínez C, Llerena A, Cobaleda J, et al. Assessment of the debrisoquin and dextromethorphan phenotyping tests by gaussian mixture distributions analysis. Clin Pharmacol Ther. 1989;45:328-33.
5. Sachse C, Brockmoller J, Bauer S, Roots I. Cytochrome P450 2D6 variants in a caucasian population: allele frequencies and phenotypic consequences. Am J Hum Genet. 1997:60:284-95.
6. Agúndez JA, Ledesma MC, Ladero JM, Benítez J. Prevalence of *CYP2D6* gene duplications and its repercussion on the oxidative phenotype in a white population. Clin Farmacol Ther. 1995;57: 256-9.
7. Rioux PP. Clinical trials in pharmacogenetics and pharmacogenomics: methods and applications. Am J Health Syst Pharm. 2000; 57:887-98.
8. Haefeli WE, Bargetzi MJ, Follath F, Meyer UA. Potent inhibition of cytochrom P450IID6 (debrisoquin 4-hydroxylase) by flecainide *in vitro* and *in vivo*. J Cardiovasc Pharmacol. 1990;15: 776-9.
9. Morike K, Magadum S, Mettang T, Griese EU, Machleidt C, Kuhlmann U. Propafenone in a usual dose produces severe side-effects: the impact of genetically determined metabolic status on drug therapy. J Intern Med. 1995;238:469-72.
10. Jazwinska-Tarnawska E, Orzechowska-Juzwenko K, Niewinski P, Rzemislawka Z, Loboz-Grudzien K, Dmochowska-Perz M, et al. The influence of CYP2D6 polymorphism on the antiarrhytthmic efficacy of propafenone in patients with paroxysmal atrial fibrillation during 3 months propafenone prophylactic treatment. Int J Clin Pharmacol Ther. 2001;39:288-92.