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ORIGINAL ARTICLE

CYP450 2D6 Genotype and Flecainide Efficacy in the Treatment of Patients with Lone Atrial Fibrillation-A Pilot Study*

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KEY WORDS: *CYP450 2D6 genotype; flecainide; atrial fibrillation; antiarrhythmic drugs*

Abbreviations
AF = atrial fibrillation
CYPP450 2D6 = cytochrome P450 2D6
EM = extensive metabolizers
IM = intermediate metabolizers
PM = poor metabolizers
UM = ultra-rapid metabolizers

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ABSTRACT

BACKGROUND Cytochrome P450 2D6 (CYP2D6) has been linked to one of four phenotypes: a) ultra-rapid metabolizers (UM), with multiple gene copies; b) extensive metabolizers (EM), with a single wild type gene copy, considered normal; c) intermediate metabolizers (IM), with decreased enzymatic activity; and d) poor metabolizers (PM) with no detectable enzymatic activity. By altering the drug dose-plasma concentration relationship, these differences may lead to severe toxicity and/or therapeutic failure.

OBJECTIVES The aim of this study was to determine the correlation between CYP2D6 polymorphisms and both efficacy and magnitude of adverse reactions of flecainide, a class IC antiarrhythmic agent.

METHODS Patients with lone atrial fibrillation (AF) were enrolled in a 2-groups prospective study: patients started on flecainide at the initial visit, then were followed up at 3 and 6 months intervals (group 1) or exhibited AF recurrences on flecainide, defined as treatment failure (group 2). Data about recurrence of AF, side effects, and demographics were collected. Genotyping was performed using AmpliChip™ CYP450.

RESULTS A total of 26 lone AF patients were enrolled (12 in group 1, and 14 in group 2). The mean age was 47± 10.8 years and 56.2 ± 10.8 years respectively. Among the analyzed phenotypes, the following distribution was found: 1/26 (3.8%) UM, 19/26 (73%) EM, 5/26 (19%) IM, 1/26 (3.8%) PM.

CONCLUSIONS In this small series of patients with lone atrial fibrillation, most patients were found to be extensive metabolizers of flecainide. There was no statistically significant correlation between the patients' genotype and flecainide efficacy / side effects.

INTRODUCTION

Flecainide is a sodium channel blocker from the class IC group in the Vaughan-Williams classification of antiarrhythmic drugs. Flecainide is metabolized by cyto-

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chrome P450 (CYP) 2D6 in the liver and is excreted by the kidneys.[1,2] The pH-dependent renal excretion of flecainide is a major route of its elimination.[3] In patients with impaired renal function or with elevated urinary pH, flecainide's elimination is dominated by hepatic metabolism.[4] The hepatic metabolism of flecainide is mediated mainly by cytochrome P450 (CYP) 2D6, which catalyses the conversion of flecainide to m-o-dealkylated flecainide (MODF), with subsequent oxidation to m-o-dealkylated lactam.[5] Flecainide is 10-fold more potent than MODF, while the m-o-dealkylated lactam has no antiarrhythmic activity.[3]

CYP2D6 has been linked to one of the following four phenotypes: a) ultra-rapid metabolizers (UM), with multiple gene copies; b) extensive metabolizers (EM), with a single wild type gene copy, considered normal; c) intermediate metabolizers (IM), with decreased enzymatic activity; and d) poor metabolizers (PM) with no detectable enzymatic activity. By altering the drug dose-plasma concentration relationship, these differences may lead to severe toxicity and/or therapeutic failure in some patients.[6,7] Tailoring the flecainide dose to the patient's genetic profile will enable clinicians to achieve optimal plasma concentration and avoid drug toxicity.

The aim of the present study was to determine the correlation between CYP2D6 polymorphisms and both efficacy and magnitude of adverse reactions of flecainide in patients with lone atrial fibrillation (AF).

METHODS

MATERIALS AND SUBJECTS

The study population included 26 patients with lone AF who were referred to the Assaf Harofeh Medical Center outpatient clinic from October 1, 2009 to April 1, 2010 (Table 1). The patients were all residents of the State of Israel and belonged to different ethnic groups. Thirteen patients were from Central or Eastern Europe, while the other 13 were from Western Europe, the Middle East or North Africa. The patients were 18 to 68 years old and had structurally normal hearts defined by echocardiography. Each patient had a history of recurrent AF more than 3 times a year prior to the initial visit. The exclusion criteria included coronary artery disease, high degree atrioventricular nodal block, presence of a permanent pacemaker, current use of antiarrhythmic drugs, a body mass index greater than 26, glucose blood levels greater than 130 mg% or the use of hypoglycemic drugs, chronic obstructive pulmonary disease or asthma, obstructive sleep apnea, prior stroke, renal failure with creatinine greater than 1.2 mg% and glomerular filtration rate <40 ml/min, elevated liver function tests 3 times the normal values, abnormal thyroid function tests, abnormal coagulation tests, neoplasm on medications, psychiatric diagnosis on medications, pregnancy and history of non-compliance.

Blood samples for genotyping were collected at the initial visit prior to initiation of any treatment. Genotyping was performed using AmpliChip™ CYP450 (Roche Molecular Diagnostics, Alameda, CA, USA). AmpliChip™ CYP450 contains more than 15,000 different oligonucleotide probes to analyze both the sense and the antisense strands of an amplified target DNA sample and provides comprehensive coverage of gene variations that play a role in the metabolism of approximately 25% of all prescription drugs. The chip genotypes accurately >99% of the world's population.[8-15]

The patients were enrolled in a 2-groups prospective study: patients started on flecainide 100 mg twice a day at the initial visit, then were followed up at 3 and 6 months intervals (group 1) or exhibited AF recurrences within one week of treatment with flecainide, defined as treatment failure (group 2). Data about recurrence of AF, side effects, and demographics were collected. A 12-lead ECG was performed at each visit. A Holter monitor was performed prior to each visit. The dose of flecainide was increased to 150 mg twice a day in patients who had AF recurrence and decreased to 50 mg twice a day in patients who developed side-effects. If side-effects persisted, flecainide was discontinued. The patients who failed flecainide therapy were enrolled in group 2 and were not seen for further follow-up. The study protocol was approved by the ethical committee of Assaf Harofeh Medical Center. Written informed consent was obtained from each patient.

STATISTICAL ANALYSIS

Data are expressed as percentages or mean ± standard deviation. The Chi-square test was used for the categorical variables and the independent sample t–test for the continuous variables. Statistical analysis was performed using an SPSS version 13 software. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 26 lone AF patients were enrolled (12 in group 1, and 14 in group 2). The mean age was 47± 10.8 years old in group 1 and significantly higher at 56.2 ± 10.8 years old in group 2. The rest of demographics parameters are summarized in Table 1. Of the analyzed phenotypes 1/26 (3.8%) patients was found to be UM , 19/26 (73%) EM, 5/26 (19%) IM and 1/26 (3.8%) PM. The CYP2D6 allele frequencies are detailed in Table 2.

Flecainide was found to be effective (no AF recurrence during the follow up period) and without side-effects in 14 /26 (53.8%) patients, effective with side-effects in 3/26 (11.5%) patients, ineffective without side-effects in 5/26 (19.2%) patients, and ineffective with side-effects in 1/26 (3.8%) patients. The 3 patients in whom flecainide was effective with side-effects had the following adverse events: one had abnormal liver

TABLE 1. Patient characteristics

	Group I (N=12)	Group II (N=14)	p value
Male gender- n (%)	7 (58.3%)	10 (71.4%)	0.48
Age-years	47.25± 10.8	56.2± 10.8	**0.04**
Age group (n, %per arm)			
<40 years old	5 (41.7%)	2 (14.3%)	0.18
41-59 years old	4 (33.3%)	4 (28.6%)	
>60 years old	3 (25.0%)	8 (57.1%)	
Smoking history –n (%)	2 (16.7)	6 (42.9)	0.14
Ethanol history –n (%)	2 (16.7)	2 (14.2)	0.86
AF Duration (years)	4.16±5.37	4.93±3.95	0.67
No. of AF Recurrences (past year)			
<10 –n (%)	7 (58.3)	8 (57.1)	0.95
>10	5 (41.7)	6 (42.9)	
Duration of AF episodes			
Minutes–n (%)	5 (45.5)	2 (15.4)	0.21
Hours	3 (27.3)	5 (38.5)	
Days	2 (18.2)	3 (23.1)	
Weeks	1 (9.1)	0	
Months	0	3 (23.1)	
Number of antiarrhythmic drugs	0.58±0.52	0.93±0.62	0.13
Number of cardioversions	0.75±1.38	1.14±1.41	0.44
Comorbidities			
None–n (%)	9 (81.8)	9 (64.3)	0.482
Hypertension	1 (9.1)	4 (28.6)	
Hyperlipidemia	1 (9.1)	1 (7.1)	
Interventricular septum width (mm)	10.36±1.63	11.62±1.61	0.07
Left atrial diameter (mm)	35.08±3.92	40.36±5.73	**0.01**
Left ventricular ejection fraction (%)	60.0	59.29±1.86	0.18
Statins–n (%)	3 (25%)	2 (14.3%)	0.49
ACE inhibitors–n (%)	3 (25%)	3 (21.4%)	0.82
Beta blockers–n (%)	5 (41.7%)	6 (42.9%)	0.95
Coumadin–n (%)	0	4 (28.6%)	**0.04**
Aspirin–n (%)	8 (66.7%)	5 (35.7%)	0.11

ACE = angiotensin converting enzyme; AF = atrial fibrillation

function tests, one had bradycardia and one had headaches which subsided when the flecainide dose was decreased from 200 mg to 100 mg daily. The patients in whom flecainide was ineffective and had side-effects complained of weakness and the drug had to be discontinued. Three (11.5%) patients were noncompliant with medical regimen. No statistically significant correlation was found between gender and drug efficacy as well as between the CYP2D6 genotype and drug efficacy or side-effects. The number of patients in the ultra-rapid metabolizers group (UM) and in the poor metabolizers group (PM) was small (one patient in each group) and therefore statistical analysis was performed only on groups containing intermediate and extensive metabolizers. Compared to group 1 patients, the patients in group 2 were found to be older with significantly enlarged left atrial diameters (Table 1). No statistical difference was found in the measured ECG intervals (PR, QRS, QT) when compared among initial, 3 months and 6 months follow-up visits.

TABLE 2. CYP2D6 Genotypes in 26 Patients with Lone AF

Phenotype (%) (Metabolizers)	Genotype	N (Male/Female)	Efficacy of Flecainide (Effective/N)	No. of patients with side effects
Ultra-rapid (UM) (3.8%)	"1/2xN"	1 (1/0)	0/1	0/1
Extensive (EM)(73%)	"1/41"	6 (4/2)	4/6	0/6
	"1/4"	2 (1/1)	1/2	0/2
	"1/1"	4 (2/2)	3/4	1/4
	"1/2 "	4 (3/1)	2/4	0/4
	"2/4"	1 (0/1)	1/1	1/1
	"2/2"	1 (1/0)	1/1	0/1
	"2/17"	1 (1/0)	0/1	0/1
Intermediate (IM) (19%)	"10/41"	2 (1/1)	1/2	0/2
	"41/41"	1 (0/1)	1/1	1/1
	"4/41"	2 (1/1)	2/2	1/2
Poor (PM) (3.8%)	"4/4"	1 (1/0)	1/1	0/1

N.B.: the different genotypes are shown in quotes

DISCUSSION

It is well known that patients respond differently to the same medication. A favorable response occurs in only 30%-70% of individuals, with a significant number of patients suffering from severe adverse drug reactions. One of the benefits of pharmacogenomics is its potential to reduce adverse drug reactions. [13] Although numerous factors (age, sex, body weight, nutrition, comorbidities, medications, infections, and/or organ function) can contribute to the variability seen in drug response, it is estimated that genetics may be one of the most important factors that accounts for 20-95% of the variability in drug disposition and effects.

There are more than 30 families of drug-metabolizing enzymes in humans, and essentially all have genetic variants, many of which translate into functional changes in encoded proteins. These enzymes are divided into phase I (predominantly oxidative) and phase II (conjugative) categories. The cytochrome P450 (CYP) enzyme system is an example of a phase I system.

Up to 23% of the population, depending on their ethnic background, has genetically determined differences in the metabolism of drugs by the CYP enzymes CYP2C9, CYP2C19, and CYP2D6.[11] More than 50% of the clinically used drugs are cleared through the action of CYP enzymes; CYP2D6 and CYP3A4 metabolize the majority of these drugs.

Patients with lone atrial fibrillation were enrolled in this study. By exclusion criteria, these were healthy patients without significant comorbidities except for hypertension. Prior studies have shown that drug metabolism can be influenced by the patient's age, sex, and genetic profile. For example, a study by Doki et al revealed clinically relevant decrease in efficacy of flecainide among male, but not female, patients.[16] In another study by the same authors, CYP2D6 genotype, as well as body weight, age, sex, and serum creatinine were shown to affect flecainide pharmacokinetics in Japanese patients with supraventricular arrhythmias.[7] Therefore, in the present study, stringent exclusion criteria were applied for patient selection in an effort to minimize effects of any such factors on flecainide's metabolism and efficacy.

In a recently published review article, Wang et al discuss the issue of genomics and drug response.[17] Specifically, they focus on cardiovascular drugs, warfarin and clopidogrel, as well as agents used for infectious disease and antineoplastic drugs. There are several prospective clinical trials investigating the value of this genetic information in patients on warfarin therapy.[18]

Tenneze et al studied the pharmacokinetics and electrocadiographic effects of a new controlled-release form of flecainide and found that the CYP2D6 polymorphism did not appear to influence flecainide disposition kinetics or electrocardiographic effects in steady state.[19] Martinez-Selles et al studied the pharmacogenetics of flecainide and propafenone in 40 patients with atrial fibrillation.[20] They found 47% poor metabolizers and 53% extensive metabolizers. Antiarrhythmic treatment was effective in 67% of patients with no difference between poor and extensive metabolizers. Adverse effects were more frequent in the poor metabolizers.

In our study, 73% of patients were extensive metabolizers of flecainide. The CYP2D6 genotype of the patients did not correlate with drug efficacy or side-effects. Although more males than females were in the EM group, statistical significance was not reached (p=0.24). The most prevalent

genotype was "1/41" which was found in 6/19 (31%) patients with an extensive metabolizer phenotype. In 4 out of these 6 patients, flecainide was effective in preventing atrial fibrillation and did not cause side-effects. Clinically, 1 patient in the extensive metabolizers group benefitted from a higher dose of flecainide, 2 patients from the intermediate group and 1 patient from the poor metabolizers group had side-effects and benefitted from a lower dose of flecainide.

STUDY LIMITATIONS

Flecainide blood levels were not processed in this study population. The correlation between blood levels of flecainide and the genetic profile could have further contributed to the understanding of the role of pharmacogenetics in this patient population. Although, according to a review article by Zhou, the large inter-individual variability in the pharmacokinetics of flecainide leads to poor correlation between daily dose and serum concentrations.[3] Additionally, the population sample size in this study was small and therefore the results cannot be extrapolated to other populations.

CONCLUSION

In this small series of patients with lone atrial fibrillation, most patients (73%) were found to be extensive metabolizers of flecainide. No statistically significant correlation was found between the patients' genotype, flecainide efficacy or side effects. A larger scale study is required to clarify the clinical importance of the genetic profile in the treatment of patients with flecainide.

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DECLARATION OF CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose

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