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Effect of CYP2D6*10 genotype on propafenone pharmacodynamics in Chinese patients with ventricular arrhythmia

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ABSTRACT

AIM: To determine the effect of CYP2D6*10 genotype on propafenone pharmacodynamics in Chinese patients with ventricular arrhythmia. **METHODS:** Seventeen Chinese patients with ventricular premature contractions (VPC≥1000/d) were recruited. They were normal in routine laboratory testing and administered propafenone hydrochloride 450-600 mg per day in three divided doses. Twelve lead cardiogram and 24 h Holter monitoring were performed before and after 7 d treatment of propafenone. Steady-state peak and trough concentrations of propafenone were measured by HPLC method. CYP2D6*10 genotypes of patients were assayed by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP). **RESULTS:** Total inhibitory rate of VPC was 79.9 % in 17 patients with ventricular arrhythmia after propafenone treatment. PR interval prolongation was increased from 0.146 s±0.018 s to 0.161 s±0.022 s (P<0.05). CYP2D6 genotypes played an important role in plasma levels and effects of propafenone. In 450 mg/d group, patients with homozygous mutant of CYP2D6*10 not only had a C_{max} of propafenone two times as high as those of wild-type genotype, but also showed a two fold higher inhibitory rate of VPC compared with those with homozygous CYP2D6*1 (P<0.05). **CONCLUSION:** CYP2D6*10 genotype is relevant to decreased activity of CYP2D6 enzyme in Chinese patients. Elevated plasma concentration is consistent with better efficacy of propafenone in patients with ventricular arrhythmia.

INTRODUCTION

Propafenone is a class Ic antiarrhythmic agent commonly used in the treatment of patients with ventricular arrhythmia. Previous work has proven that propafenone undergoes stereoselective metabolism, with *R*-enantiomer being eliminated faster than *S*-enantiomer[1,2]. Genetic polymorphism of CYP2D6 has demonstrated significant impact on pharmacokinetics and pharmacodynamics of propafenone. Our previous study has found that CYP2D6 phenotype determines the pharmacokinetic variability of propafenone enantiomer, existence of intermediate metabolizer (IM) may be relevant to diminished capacity of CYP2D6 enzyme in Chinese subjects[3]. In our another report on simultaneous modeling of pharmacokinetics and pharmacodynamics of propafenone, it has been shown that CYP2D6 phenotype may influence not only kinetic properties but also pharmacological effects of propafenone at the same time[4]. However, Labbe *et al* found that

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CYP2D6 phenotype had very little impact on the pattern of ECG parameters in 15 healthy men who administered propafenone[5]. It is worthwhile to notice that all these studies were done in healthy subjects and phenotyping of CYP2D6 in patients possess ethical and interfering problems if they are lying in bed and taking other drugs knowing to induce or inhibit CYP2D6. Genotyping is a new method with high accuracy and reliability in predicting CYP2D6 activity of patients. We have developed a genotyping method based on PCR and RFLP, which identified CYP2D6*10 genotype in Chinese subjects with decreased enzyme activity[6]. There has been no report on CYP2D6 genetic polymorphism of propafenone and pharmacodynamics in patients with ventricular arrhythmia. The purpose of this study was to assess the effect of CYP2D6*10 genotype on propafenone pharmacodynamics in 17 Chinese patients with ventricular arrhythmia.

MATERIALS AND METHODS

Subjects Seventeen patients (13 men and 4 women) with ventricular premature contractions (VPC≥ 1000/d) were recruited from our hospitals. Their average age was (49±5) a, and their mean body weight (67±8) kg (Tab 1). All patients had normal hepatic and renal functions as assessed by biochemical testing. Thoracic *X*-ray and ultrasonic cardiogram excluded patients with severe cardiac dysfunction. This study was approved by the Ethic Committee in our hospital. Written informed consent was obtained from all patients before study.

Study protocol After all cardiac active drugs had been withdrawn for a period of time more than five half-life, patients received an oral dose of propafenone hydrochloride (Xinyi Pharmaceutical Company, Shanghai, China) at a dose of 150-200 mg every 8 h for consecutive 7 d. Twelve-lead electrocardiogram (ECG, 9320 K cardiograph, Japan Photoelectronics Company, Japan) and 24 h Holter (43420B Holter, HP company, USA) monitoring were performed at baseline (no drug) and at the 7th day after drug treatment. Steady-state peak and trough concentrations of propafenone were obtained 2 h after and immediate before the 7th day administration of drug. Plasma was separated and stored at –20 °C for drug analysis.

Data analysis Holter was used to observe inhibitory rate of ventricular premature contractions according to formula below:

$$E\% = (E_0 - E_t) / E_0 \times 100\ \%$$

Tab 1. Demographic data of patients with ventricular arrhythmia.

Subject	Sex	Age/ a	Weight/ kg	Diagnosis	Dosage/ mg	CYP2D6 Genotype
1	Male	60	68	VPC	450	*10/*10
2	Male	33	64	VPC	600	*10/*10
3	Male	60	62	Hypertension VPC	450	*1/*1
4	Female	60	67	VPC	450	*1/*10
5	Male	36	69	VPC	450	*1/*10
6	Male	43	75	VPC	600	*1/*10
7	Male	68	67	Hypertension VPC	450	*10/*10
8	Male	44	70	VPC	600	*1/*10
9	Female	61	67	VPC	450	*10/*10
10	Female	35	53	VPC	450	*10/*10
11	Male	37	60	VPC	450	*10/*10
12	Male	50	75	VPC	450	*1/*1
13	Female	28	52	VPC	450	*10/*10
14	Male	65	75	VPC	450	*1/*10
15	Male	22	62	VPC	450	*1/*1
16	Male	57	66	VPC	450	*1/*10
17	Male	69	83	Hypertension VPC	600	*1/*10

VPC: ventricular premature contractions.

Where E_0 represents VPC before propafenone treatment, E_t is VPC after treatment. $E\%$≥75 % is regarded as effective. HR (heart rate), PR, QRS, and QT intervals were determined directly from ECG as an average value of 10 measurements.

Determination of propafenone concentrations Plasma propafenone concentrations were analyzed by a modified HPLC method as described before[7]. The solvent delivery system was a Shimadazu pump model LC-6A. The analytical column was a Hypersil ODS (200 mm×4.6 mm, 5 μm particle size), and column effluent was monitored with SPD-6AV ultraviolent spectrophotometric detector (Shimadzu Coop, Japan) at 208 nm. The mobile phase was a mixture of acetonitrile, water, and acetic acid (60:40:0.01; v:v:v). The flow rate was set at 1.0 mL/min. We used the sum of *S*- and *R*-propafenone as total propafenone level.

Determination of CYP2D6*10 genotype CYP2D6 genotype of patients were determined by PCR and RFLP techniques established in our lab[6]. DNA was extracted from whole blood by a modified phenol/ chloroform method. PCR was employed to amplify a

433 bp gene fragment, which was subsequently digested with *Hph* I restriction enzyme to test the presence of CYP2D6*10 mutant allele. There were always positive and negative controls to verify the accuracy of genotype.

Statistical analysis The differences in propafenone concentrations and pharmacodynamic parameters between different CYP2D6 genotypes were tested by unpaired *t* test. A *P* value less than 0.05 was considered as significant. Data were expressed as mean±SD.

RESULTS

Total inhibitory rate of ventricular premature contractions (VPC%) was 79.9 % in average in 17 patients after daily administration of 450-600 mg of propafenone hydrochloride for consecutive 7 d. The inhibitory rate of VPC in 600 mg/d group (n=4) was significantly higher than that in 450 mg/d group (n=13) (99.93 %±0.12 % *vs* 75 %±42 %, P<0.05). PR interval prolongation was increased from 0.146 s±0.018 s to 0.161 s±0.022 s (P<0.05) at the same time. The average percent of PR interval increase was 10.5 %. However, there were no significant changes in HR, QRS, and QT interval after drug treatment.

The distribution of CYP2D6 genotypes in 13 patients of 450 mg/d group were divided into three groups: homozygous wild-type *1/*1 (n=3), heterozygous *1/*10 (n=4), and homozygous mutant *10/*10 (n=6) (Tab 1). A comparison of propafenone concentrations (C_{max} and C_{min}) with CYP2D6*10 genotypes was shown in Fig 1. C_{max} in *10/*10 group was significantly higher than that in *1/*1 group (233 μg/L±73 μg/L *vs* 125 μg/L±38 μg/L, P<0.05). There were also significant difference of propafenone C_{max} between *10/*10 and *1/*10 genotypes (P<0.01). Although comparisons of HR, PR, and QRS intervals among three CYP2D6 genotypes showed no significant differences (P>0.05), VPC% in *10/*10 group was about twice as much as that in *1/*1 group (96 %±6 % *vs* 58 %±34 %, P<0.05). There were also significant differences of QT intervals between *1/*1 and *1/*10 groups or between *1/*10 and *10/*10 groups (P<0.05, Tab 2).

DISCUSSION

CYP2D6 exists significant genetic polymorphism in various ethics. The frequency of the poor metabolizer (PM) is reported to be 7 % in Caucasians[8]. However, PM in Asians including Chinese, Japanese, and Koreans is less than 1 %[8-10]. The CYP2D6*10 allele has

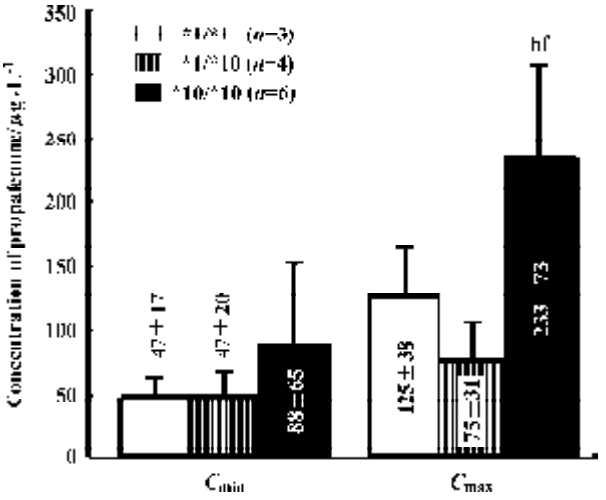

Fig 1. Relationship between CYP2D6 genotypes and plasma concentrations of propafenone after a daily dose of 450 mg in 13 Chinese patients with ventricular arrhythmia. Mean±SD. [b]P<0.05 *vs* *1/*1. [f]P<0.01 *vs* *1/*10.

Tab 2. Relationship between CYP2D6 genotype and pharmcodynamic parameter (% ECG & VPCs) of propafenone after a daily dose of 450 mg in 13 patients with ventricular arrhythmia. Mean±SD. [b]P<0.05 compared with *1/*1. [e]P<0.05 compared with *1/*10.

CYP2D6	n	HR/%	PR/%	QRS/%	QT/%	VPC/%
*1/*1	3	3.5±1.9	5±8	–3±6	5.2±0.8	58±34
*1/*10	4	–3±9	8±11	–3±9	–7±6[b]	58±71
*10/*10	6	–2.8±5.6	13±4	1.5±9.8	3±4[e]	96±6[b]

been associated with reduced metabolic activity in the extensive metabolizers (EM) on Asian subjects. Huang *et al*[11] has found that pharmacokinetics of metoprolol enantiomers is related to CYP2D6*10 genotypes in Chinese subjects. Subjects with T_{188} mutation (a indicator of CYP2D6*10 allele) had higher metoprolol plasma concentrations and lower urinary metoprolol metabolite level. Mihara *et al*[12] indicated that CYP2D6*10 allele plays an important role in the metabolism of haloperidol and reduced haloperidol in Japanese patients with schizophrenia. The concentration of haloperidol in the patients with 0, 1, and 2*10 alleles were (22.8±11.0), (30.1±10.6), and (31.2±21.2) nmol/L, respectively. Yoon *et al*[13] has shown that the EM with CYP2D6*10 allele seemed to have higher plasma concentrations of paroxetine than those with wild-type genotype in 16 Korean subjects. The AUC of paroxetine in EM with

*10/*10 genotype (666.4±169.4) ng·mL·h^{-1} was significantly higher than that of EM with *1/*1 genotype (194.5±55.9) ng·mL·h^{-1}.

In this study, effective rate of 600 mg/d group was much higher than that of 450 mg/d group, indicating a dose-dependent trend in the efficacy of propafenone. However, plasma concentrations of propafenone at peak and trough time varied in different patient at the same dose. There are no correlation between C_{max} or C_{min} of propafenone and electrocardiographic parameters (PR, QRS, and QT intervals). It may result from both pharmacokinetic variability and genetic polymorphism of CYP2D6. Therefore, it is difficult to estimate propafenone efficacy if only based on either plasma concentration or ECG changes of propafenone in patients with ventricular arrhythmia.

The total inhibitory rate of VPC was 80 %±42 % (range: -48 %-100 %) after 7 d treatment of propafenone in 17 patients with ventricular arrhythmia, which shows good inhibitory effect of propafenone on VPC. Moreover, CYP2D6 genotype has an important role in determining plasma concentration and antiarrhythmic effect of propafenone. In 450 mg/d group, patients with CYP2D6 *10/*10 genotype not only has its C_{max} about twice as high as those with CYP2D6 *1/*1 genotype, but also shows greater inhibitory effect (VPCs) (96 %±6% *vs* 58 %±34 %, P<0.05). Therefore, to our knowledge, it is the first report evaluating the relationship between CYP2D6*10 genotype and propafenone plasma concentrations and/or pharmacodynamics.

In conclusion, CYP2D6*10 genotype is highly relevant to both increases of peak plasma concentrations and efficacy of propafenone. The further study on the effect of CYP2D6 genetic polymorphism on pharmacodynamics of propafenone and other drugs may provide invaluable information to predict clinical effect and toxicity in patients.

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