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CYP2D6 phenotype determines pharmacokinetic variability of propafenone enantiomers in 16 HAN Chinese subjects[1]

CAI Wei-Min[2], CHEN Bing[3], CAI Ming-Hong[3], ZHANG Yin-Di
(*Institute of Clinical Pharmacology, Nanjing Medical University; [3]Department of Clinical Pharmacology, Nanjing General Hospital of Nanjing Command, Nanjing 210002, China*)

KEY WORDS propafenone; stereoisomerism; high pressure liquid chromatography; pharmacokinetics; cytochrome P-450 CYP2D6; phenotype; Mongoloid race

ABSTRACT

AIM: To determine the role of the CYP2D6 phenotype in the metabolism of propafenone (Pro) enantiomers in 16 HAN Chinese subjects. **METHODS**: Seven very extensive metabolizers (VEM) and nine intermediate metabolizers (IM) were enrolled from a Chinese population whose phenotype had been previously assessed with a dextromethorphan metabolic phenotyping. The blood samples (0 – 15 h) were taken after oral administration of a single dose (400 mg) of rac-Pro hydrochloride. Enantiomeric concentrations of propafenone in plasma were measured by a reverse-phase HPLC with precolumn derivatization. **RESULTS**: *S*-Pro was less metabolized and had higher plasma concentrations than *R*-Pro in both CYP2D6 phenotypes. Besides, the $T_{1/2}$ of *R*-Pro was longer than that of *S*-Pro in IM, but not in VEM. However, there were significant differences in the metabolism of Pro enantiomers between VEM and IM. The C_{max} and AUC of both isomers in the IM group were higher than those in the VEM group ($P < 0.01$). The *Cl* of Pro enantiomers in IM group was only about half of that in VEM group [(67 ± 17) *vs* (133 ± 28) L·h^{-1} for *S*-Pro, (90 ± 24) *vs* (200 ± 87) L·h^{-1} for *R*-Pro, $P < 0.01$]. The *S*/*R* ratios of $T_{1/2}$, T_{max}, C_{max}, *Cl*, and AUC were not significantly different ($P > 0.05$). **CONCLUSION**: CYP2D6 phenotype determines the pharmacokinetic variability of propafenone enantiomers and existence of IM may be relevant to diminished capacity of CYP2D6 enzyme in Chinese subjects.

INTRODUCTION

Propafenone (Pro) is a commonly used anti-arrhythmic agent which is effective in the management of atrial and ventricular arrhythmias. Pro is clinically used as a racemic mixture of *S*-Pro and *R*-Pro[1]. Pro undergoes stereoselective pharmacodymamics and pharmacokinetics *in vivo*. Although both enantiomers exhibit the similar sodium-channel blocking effect, the β-blocking activity resides in the *S*-Pro which accounts for some of the side effects in patients[2]. The two enantiomers are metabolized at different rates, with the *R*-Pro being eliminated faster than the *S*-Pro[3].

Pro is biotransformed mainly through cytochrome P-450 CYP2D6 (CYP2D6) to the active metabolites (5-OH Pro) and less extensively through CYP3A4 to *N*-desalkyl Pro. Previous work has proven that its metabolism is polymorphic and genetically determined, *ie*, about 7 % of Caucasians characterized as poor metabolizers (PM) of CYP2D6[4]. However, PM in Chinese (about 1 %) is lower compared with Caucasians[5]. Furthermore, our recent research on dextromethorphan metabolic phenotyping in Chinese population has shown that Chinese extensive metabolizers (EM), which consist of 99 % of the Chinese population, could be further divided into very extensive metabolizers (VEM) and intermediate metabolizers (IM)[6]. The purpose of this study was to examine the metabolism of propafenone enantiomers in 16 Chinese subjects with VEM and IM phenotypes of

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[2] Correspondence to Dr CAI Wei-Min. Phn 86-25-482-8619. E-mail wmcai@public1.ptt.js.cn
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CYP2D6 to determine if stereoselective pharmacokinetics of propafenone would occur and whether the metabolism of propafenone enantimers would depend on the CYP2D6 phenotype in Chinese subjects.

MATERIALS AND METHODS

Subjects This study was performed according to the Helsinki Declaration and approved by the Ethics Committee at our hospital. Informed consent was obtained from all subjects. Therefore, 16 healthy subjects of HAN Nationality (10 men and 6 women, age from 23 to 45 a; weight range, 50 to 75 kg) were recruited from our previous study population of 120 volunteers undergoing the dextromethorphan metabolic phenotyping of CYP2D6[6]. Seven subjects (4 men, 3 women) were classified as VEM ($\lg MR \leq -1.81$), and 9 subjects (6 men, 3 women) as IM ($-1.81 < \lg MR < -0.52$). All subjects were healthy as assessed by the medical history, physical examination, ECG, and routine laboratory testing. All were non-smokers and drug free for at least 2 wk before and during the study.

Protocol After an overnight fast, subjects received 400 mg rac-propafenone hydrochloride tablets (Xingyi Pharmaceutical Company, Shanghai, China, Lot № 96100037) orally. An intravenous catheter (B Braun, Melsungen, Germany, 1.1 mm × 33 mm) was inserted into the vein in either arm of each subject, and blood samples were drawn at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 15 h after administration. Plasma was separated from heparin anticoagulated tube, and stored at −20 ℃ until the assay. ECG (Cardiofax, model 6511, Shanghai Kohden Med Electronic Instrument Corporation, China), heart rate and blood pressure pertinent to clinical effects of propafenone were assessed at baseline and at 1, 2, 3, 4, 6, 8, and 15 h.

Drug analysis Pro enantiomers were determined by a reverse-phase high performance liquid chromatography (HPLC) established in our laboratory[7], with some modification to extend the lower limit of quantitation. Briefly, plasma 1 mL was extracted with 5 mL hexane-iospentanol (99∶1) after alkalization. Pro was subjected to react with 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyransoyl isothiocyanate (GITC, Sigma Chemical Co, USA) for 1 h at 20 ℃. The resulting diastereoisomers were injected onto an achiral Hypersil ODS column (4.6 mm × 20 cm, 5 μm). The HPLC system comprised of an LC-6A pump, a SPD-6AV UV detector and a C-R6A integrator (Shimadzu Corporation, Japan). The enantiomers were eluted with acetonitrile-water-acetic acid (60∶40∶0.01) at a flow rate of 1 $mL \cdot min^{-1}$, and detected under 208 nm. The limit of detecting *S*-Pro and *R*-Pro was 10 $\mu g \cdot L^{-1}$ and 13 $\mu g \cdot L^{-1}$, respectively. The average intraday and interday CV were all below 6 %, and average recovery was 102.2 %.

Data analysis The pharmacokinetic parameters ($T_{1/2}$, C_{max}, T_{max}) of propafenone enantiomers were obtained from a PKBP-N1 computer program with one-compartment simulation[8]. Area under the plasma concentration-time curve (AUC) was determined by the trapezoidal rule and extrapolated to infinity by calculation as C_t/k, where C_t was the last plasma concentration determined at 15 h. The apparent oral clearance (Cl) was calculated as dose/AUC. The differences in the pharmacokinetics between *S*-Pro and *R*-Pro were tested by the t test for paired samples, while the differences in the pharmacokinetics of both enantiomers between VEM and IM were tested by unpaired t test. Data were expressed as $\bar{x} \pm s$.

RESULTS

Fig 1 shows the plasma concentration-time profile of propafenone enantiomers in 7 VEM and 9 IM of CYP2D6 in Chinese healthy subjects over 15 h after a single oral dose (400 mg) of rac-Pro hydrochloride. There were significant differences in the stereoselective disposition between VEM and IM in both *S*-Pro and *R*-Pro group (Fig 1).

For VEM group, the C_{max} and AUC of *S*-Pro were significantly higher than those of *R*-Pro ($P < 0.01$), and clearance of *S*-Pro was lower than that of *R*-Pro ($P < 0.05$). For IM group, the AUC and C_{max} of *S*-Pro were remarkably higher than that of *R*-Pro ($P < 0.01$) and Cl of *S*-Pro was significantly lower than that of *R*-Pro ($P < 0.01$). Besides, half-life of *R*-Pro was prolonged as compared with that of *S*-Pro in IM group (3.1 ± 0.9 *vs* 2.6 ± 0.6 h, $P < 0.05$), indicating a stereoselective metabolism observed in IM, but not in VEM.

The CYP2D6 phenotype played an important role in the metabolism of propafenone enantiomers. The

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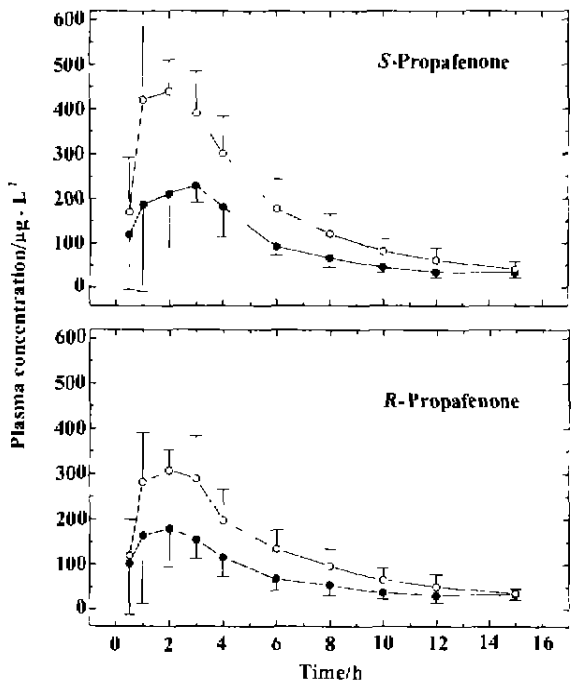

Fig 1. Plasma concentration-time profile of propafenone enantiomers among 7 VEM(●) and 9 IM (○) of CYP2D6 phenotype.

C_{max} and AUC of both enantiomers in IM group were obviously greater than those in VEM group ($P < 0.01$), whereas the clearance of *S*-Pro and *R*-Pro in IM group was only about half of clearance in VEM group [(67 ± 17) *vs* (133 ± 28) L·h^{-1} for *S*-Pro, (90 ± 24) *vs* (200 ± 87) L·h^{-1} for *R*-Pro, $P < 0.01$]. The *S*/*R* ratios of $T_{1/2}$, T_{max}, C_{max}, *Cl*, and AUC were not significantly different between VEM and IM ($P > 0.05$) (Tab 1).

The electrocardiographic (ECG) monitoring in 16 Chinese subjects revealed that there were no differences in heart rate and blood pressure between VEM and IM group. The prolongation of the QRS complex, an *in vivo* marker of sodium-channel blockade, ranged from 10 – 100 % of the baseline values in two phenotypes. However, there was no difference in the % change of QRS between VEM and IM at the time observed ($P > 0.05$). The intake of propafenone was associated with dizziness in 4 subjects (1 in VEM, 3 in IM).

DISCUSSION

The debrisoquine hydroxylation (CYP2D6) polymorphism is one of the most active research area as many of its substrates (including propafenone) have a narrow therapeutic index and marked inter-individual variability in pharmacokinetics and pharmacodynamics. The relationship between stereoselectivity and metabolism of CYP2D6 substrates has been found for many drugs in Caucasians such as metoprolol[9] and carvedilol[10], indicating various effects of CYP2D6 phenotype on the disposition of these drug isomers.

It has been shown that Chinese subjects are more vulnerable to side-effects of CYP2D6 substrates[11]. Horai *et al* found that frequency distribution curve for metoprolol metabolic phenotype in Chinese population was skewed to the right compared with that in Japanese population, suggesting more IM in the Chinese population[12]. Hou *et al* reported that 44 % of the Chinese subjects were classified as IM by urinary analysis of dextromethorphan phenotype[13]. Our previous study utilizing also dextromethorphan as probe has successfully categorized Chinese in mainland, China into 63 % of VEM, 36 % of IM, and 1 % of PM subgroups by a mathematical model of Gram-Charlier series[6].

Propafenone undergoes stereoselective disposition and is subjected to a genetic polymorphism in its metabolism. Kroemer *et al* demonstrated that stereoselective disposition of propafenone enantiomers is phenotype dependent, with *R*-Pro cleared faster than *S*-Pro in Caucasian EM patients as compared with PM

Tab 1. Pharmacokinetic parameters of propafenone enantiomers after a single dose (400 mg) of propafenone hydrochloride in two CYP2D6 phenotypes. $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* *S*-Pro. $^fP < 0.01$ *vs* VEM.

Parameters		*n*	*S*-Pro	*R*-Pro	*S*/*R* ratio
$T_{1/2}$/h	VEM	7	2.5 ± 0.7	2.4 ± 0.9	1.10 ± 0.37
	IM	9	2.6 ± 0.6	3.1 ± 0.9^b	0.86 ± 0.15
T_{max}/h	VEM	7	2.0 ± 0.9	2.0 ± 1.0	1.08 ± 0.19
	IM	9	1.6 ± 0.8	1.5 ± 0.8	1.06 ± 0.15
C_{max}/μg·L^{-1}	VEM	7	295 ± 136	212 ± 119^c	1.46 ± 0.23
	IM	9	504 ± 74^f	353 ± 57^{fb}	1.45 ± 0.24
Cl/L·h^{-1}	VEM	7	133 ± 28	200 ± 87^b	0.69 ± 0.19
	IM	9	67 ± 17^f	90 ± 24^{fc}	0.75 ± 0.07
AUC/	VEM	7	1501 ± 299	1087 ± 396^c	1.5 ± 0.3
μg·h·L^{-1}	IM	9	2769 ± 588^f	2067 ± 457^{fc}	1.35 ± 0.12

patients[12]. Volz *et al*, however, found that neither a genetic disposition (gender, metabolic phenotype) nor age or the dose applied had any influence on the measured plasma isomer ratio in Caucasian patients[13]. For Chinese, especially Chinese in mainland, China, studies on the enantiomeric disposition of propafenone and relation to the CYP2D6 phenotype are limited. Kuang *et al* studied propafenone pharmacokinetics in Chinese volunteers with 8 EM and 1 PM of debrisoquine[14]. Although there seemed to have great difference of pharmcokinetic parameters ($T_{1/2}$, AUC, Cl) between two phenotypes, no statistically definite conclusion could be drawn as only 1 PM involved. Zhong *et al* investigated only stereoselective pharmacokinetics of propafenone enantiomers in 10 healthy Chinese subjects[15]. Therefore, to our knowledge, this is the first investigation that describes the role of the genetically determined CYP2D6 activity in the disposition of propafenone enantiomers in Chinese subjects. We found that S/R ratio of C_{max}, AUC, and Cl for propafenone enantiomers were around 1.22 – 1.46, 1.35 – 1.47, and 0.69 – 0.75 in two CYP2D6 phenotypes-indicating preferential elimination of R-Pro in Chinese. At the same time, we found that $T_{1/2}$ of R-Pro was higher than that of S-Pro in IM, but not in VEM. Thus, CYP2D6 phenotype has the effect on the stereoselective disposition of Pro. CYP2D6 phenotype also played a significant role in the metabolism of propafenone. The C_{max} and AUC of both enantiomers in IM group were about two-fold higher than those in VEM group, whereas the Cl of both enantiomers in IM group was only half of Cl in VEM group. Our study suggests that CYP2D6 phenotype determines pharmacokinetic variance of propafenone in Chinese subjects. Thus, IM of CYP2D6 in Chinese may be at increased risk of side-effects to propafenone and other drugs metabolized by CYP2D6. Identification of these slower metabolizers in Chinese patients would be of importance in the individualization of drug therapy.

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CYP2D6 表现型决定 16 名中国汉族受试者普罗帕酮对映体药物动力学的差异[1]

蔡卫民[2]，陈 冰[3]，蔡明虹[3]，张银娣
（南京医科大学临床药理研究所；[3]南京军区南京总医院临床药理科，南京 210002，中国）

关键词 普罗帕酮；立体异构；高压液相色谱；药物动力学；细胞色素 P-450 CYP2D6；表型；蒙古人种

目的：研究 CYP2D6 表现型在汉族健康受试者普罗帕酮对映体代谢中的作用. **方法**：选取用右美沙芬进行代谢分型后得到的 7 名极快代谢者（VEM）和 9 名中速代谢者（IM）. 单剂量口服消旋普罗帕酮 400 mg，抽取 0－15 h 静脉血. 运用反相高压液相色谱法加柱前衍生化，定量分析血浆中普罗帕酮对映体浓度. **结果**：两种 CYP2D6 表现型的 *S*-Pro代谢均较 *R*-Pro 慢，血浆浓度升高. 此外，IM 中 *R*-Pro 的半衰期比 *R*-Pro 大，VEM 无此差别，但是，Pro 对映体在 VEM 和 IM 中的代谢有明显差异. IM 组两种对映体的 C_{max} 和 AUC 均比 VEM 组大（$P<0.05$）. IM 组 Pro 对映体的 Cl 仅为 VEM 组的一半[(67±17) *vs* (133±28) $L\cdot h^{-1}$ for *S*-Pro, (90±24) *vs* (200±87) $L\cdot h^{-1}$ for *R*-Pro, $P<0.01$]. $T_{1/2}$、T_{max}、C_{max}、Cl 和 AUC 的 *S*/*R* 比值无显著差异（$P>0.05$）. **结论**：CYP2D6 表现型决定了普罗帕酮对映体的药动学差异，EM 受试者中 IM 的存在也许与中国人 CYP2D6 酶活性下降有关.

（责任编辑 朱倩蓉）

首届“中国药学科学发展战略”中青年学者学术研讨会纪要

1999 年 5 月 4－6 日，首届“中国药学科学发展战略”中青年学者学术研讨会在上海隆重举行. 该研讨会由国家自然科学基金委员会主办，中国科学院上海药物研究所承办. 国家自然科学基金委员会袁海波秘书长和国家药品监督管理局副局长桑国卫等领导与会并作了重要讲话. 会议正式代表 100 人，为具有博士学位或副教授以上职称、工作上承担过国家自然科学基金等项目、学术上已形成自己研究领域和方向的中青年学者. 杨胜利院士、桑国卫研究员，陈凯先研究员和郭跃伟研究员分别就人类基因组计划、中国新药临床试验、创新药物的重点基础研究项目和欧洲海洋药物研究现状及对我国海洋药物开发的启示在大会作了重要报告；台湾大学医学院胡幼圃教授介绍了我国台湾省跨世纪药学科学的发展规划. 58 位代表在分会会场报告，共同探讨了面向 21 世纪的中国药学科学发展战略，并包括“十五”计划的重大和重点项目设想、优先资助领域问题. 会议提出今后我国新药发展方向主要为：抗高血压药物，抗肿瘤药物、非成瘾性镇痛药等，重点开发反义核苷酸，肿瘤血管生成抑制剂，离子通道药物，神经细胞保护药等. 会议还讨论了新药研究的若干基础问题：

（1）药物基因组学. 寻找基因型药物，基因与药物代谢动力学，基因工程在中药研究中的作用.

（2）计算机技术与新药创新. 各种理论计算方法和分子图形模拟技术辅助药物设计.

（3）药物先导化合物的来源. 天然产物，着重于海洋药物、微生物、真菌产物等；基因、细胞工程产物；合成、半合成化合物，着重于组合化学库.

（4）药物筛选有关的基础研究. 以靶的三维空间结构为基础，筛选或设计与靶结构互补、具有治疗作用的小分子化合物是当前新药研究中最具挑战性的研究内容.

（5）新药研究的新方法和新技术.

会议还对中药现代化的基础研究若干问题进行了探讨，重点讨论了资源、质量、中药理论、中药及其活性成分的作用机制等. 会议正式出版了论文集《中国药学科学发展战略与新药研究开发》.