ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 Oct; 22 (10): 956-960
http://www.chinaphar.com

Simultaneous modeling of pharmacokinetics and pharmacodynamics of propafenone in healthy subjects

CAI Wei-Min[1], ZHANG Yin-Di[2], CHEN Bing[3], CAI Ming-Hong[3], LUO Jian-Ping, LING Shu-Sen[3]
(*Institute of Clinical Pharmacology, Nanjing Medical University*; [3]*Department of Clinical Pharmacology, Jinling Hospital, Nanjing 210029, China*)

KEY WORDS propafenone; pharmacokinetics; models; cytochrome P-450 CYP2D6

ABSTRACT

AIM: To study the simultaneous modeling of pharmacokinetics and pharmacodynamics (PK-PD) of propafenone (Pro) in healthy subjects. **METHODS**: Ten healthy Chinese volunteers, 5 extensive metabolizers (EM) and 5 intermediate metabolizers (IM) of CYP2D6, received a single dose (400 mg) of Pro hydrochloride. The blood samples and electrocardiogram (ECG) measurements were taken after administration over 15 h period. The concentrations of Pro in plasma were measured by a reverse-phase HPLC. PR interval was used as an average value of 10 PR interval measurements. **RESULTS**: There was a delay between Pro level and percentage of PR interval prolongation. After PK-PD simulating, the relationship between effect concentration (Ce) and the effect met the sigmoid E_{max} model. CYP2D6 (EM & IM) played an important role in both pharmacokinetics and pharmacodynamics which produced by Pro. The AUC ($\mu g \cdot h \cdot L^{-1}$) of IM group was significantly higher than that of EM group (5126 ± 1030 *vs* 2948 ± 1230, $P < 0.05$). Whereas Ce_{50}($\mu g/L$) was also greater in IM group than in EM group (747 ± 281 *vs* 359 ± 123, $P < 0.05$). On the other hand, γ of EM group was about one fold larger than that of IM group ($P < 0.05$). **CONCLUSION**: CYP2D6 phenotype of human may influence not only pharmacokinetic of Pro but also its pharmacological effects.

INTRODUCTION

Propafenone (Pro) is an Ic class antiarrhythmic agent, which possesses an effect of blocking sodium-channel *in vivo*. It has been established that Pro undergoes stereoselective pharmacokinetics and its variability is determined by CYP2D6, an enzyme responsible to Pro metabolism in human[1,2]. There are greater inter-individual variances in clinical dosage to achieve a safe and efficient effect. Whether it is related to pharmacokinetic and/or pharmacodynamic variability needs to be clarified. Simultaneous modeling of pharmacokinetics and pharmacodynamics (PK-PD modeling) has emerged as a new approach to deal with some clinically important and wildly used drugs. PK-PD modeling expands classic pharmacokinetics by suggesting a hypothetical effect compartment, which relates drug concentration to level in effect compartment and finally to drug effect[3]. The purpose of this study was to investigate the relationship between plasma concentration and PR interval prolongation with a PK-PD modeling in 10 healthy subjects after administration of 400 mg of propafenone hydrochloride.

MATERIALS AND METHODS

Subject Ten healthy HAN Chinese subjects (5 men and 5 women) were recruited. Their average age was (35.3 ± 6.0) a and weight (60.0 ± 5.5) kg. Five (3 male, 2 female) subjects were extensive metabolizers (EM) of CYP2D6 and five (2 male, 3 female) intermediate metabolizers (IM) according to CYP2D6 phenotype established in our lab[4]. All subjects were healthy as assessed by the medical history, electrocardiogram (ECG) and biochemical testing. All were non-smokers and drug free for at least 2 weeks before and during the study.

Protocol After an overnight fasting, subjects received 400 mg propafenone hydrochloride tablets

[1] Now doing postdoctoral fellow in *College of Pharmacy, University of Kentucky, USA*.
Phn 1-859-246-7692. E-mail weimincai@hotmail.com
[2] Correspondence to Prof ZHANG Yin-Di. Phn 86-25-666-2883. E-mail ydzhang@njmu.edu.cn
Received 2001-01-22 Accepted 2001-07-01

(Xingyi Pharmaceutical Company, Shanghai, China, Lot No 9610037) orally. Blood was taken at 0.5, 1, 2, 3, 4, 6, 8, 15 h after drug administration. Plasma was separated and stored at − 20 ℃ until assay. ECG (Cardiofax, model 6511, Shanghai Kohden Medical Electronic Instrument Corporation, China) was assessed at each blood drawing. PR interval, a significant and regulatory index pertinent to pharmacological effect of Pro, was used as an average value of 10 PR interval measurements.

Drug analysis Plasma Pro concentrations were measured by a reverse-phase high performance liquid chromatography[2] (HPLC pump: Shimadzu LC-6A, SPD-6AV ultraviolent spectrophotometric detector 208 nm; column: hypersil ODS 200 mm × 4.6 mm, 5 μm; mobile phase: acetonitrile : water : acetic acid = 60 : 40 : 0.01; flow rate: 1.0 mL/min) established in our lab[5]. We used the sum of *S*-Pro and *R*-Pro as total Pro level.

Data analysis PK-PD modeling of Pro was undertaken by a CAPP program (Computer Aids Pharmacokinetic and Pharmacodynamic modeling, developed by Nanjing Medical University, China)[6] to simulate Pro plasma concentrations with percentage of PR interval prolongation. A model of first-order rate absorption and two plus effect compartment was used after orally pro administration. A sigmoid E_{max} model was utilized in the final pharmacodynamic modeling:

$$E(t) = \frac{E_{max} \cdot Ce(t)^{\gamma}}{Ce_{50}^{\gamma} + Ce(t)^{\gamma}}$$

Where E is effect, Ce is the concentration of Pro in effect compartment, E_{max} is the maximum effect, Ce_{50} is the Pro level at 50 % of E_{max}, γ is sigmoid parameter of effect curve. The differences in the pharmacokinetic and pharmacodynamic parameters between different CYP2D6 phenotypes were tested by unpaired t test. A P value less than 0.05 is considered as significant.

RESULTS

Fig 1 shows the plasma concentration-time curve of Pro in 10 healthy subjects over 15 h after a single oral dose of 400 mg Pro hydrochloride. The Pro effect-time curve is shown in Fig 2. By simulating average Pro level to percentage of PR interval prolongation with CAPP program, we found that there was a delay between effect and level of Pro (Fig 3A). The concentration-effect curve was connected with central compartment (Fig 3B), a relationship between effect concentration (Ce) and effect is found to meet Sigmoid E_{max} model (Fig 3C). Fig 3D is a simulating curve of Pro effect versus time.

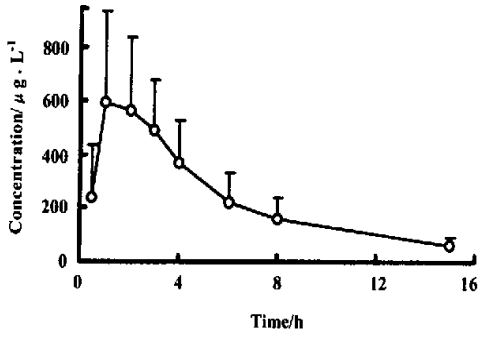

Fig 1. Plasma concentration-time curve of propafenone in 10 healthy Chinese subjects. $\bar{x} \pm s$.

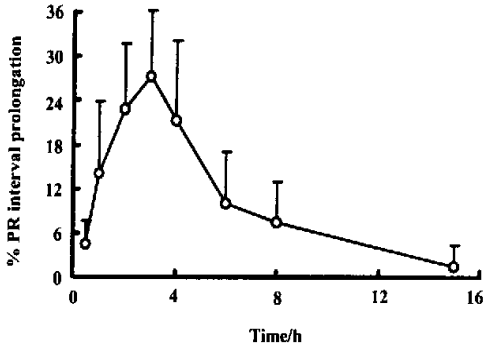

Fig 2. Effect-time curve of propafenone in 10 healthy Chinese subjects. $\bar{x} \pm s$.

Pharmacokinetic and pharmacodynamic parameters simulated by CAPP program in 10 healthy subjects are shown in Tab 1 and 2. The parameters by comparisons with different CYP2D6 phenotypes (EM & IM) are summarized in Tab 3 and 4. The AUC ($\mu g \cdot h \cdot L^{-1}$) of IM group is significantly higher than that of EM group (5126 ± 1030 *vs* 2948 ± 1230, $P < 0.05$). Whereas Ce_{50}($\mu g/L$) is also greater in IM group than that in EM group (747 ± 281 *vs* 359 ± 123, $P < 0.05$). On the other hand, γ (a parameter of sigmoid effect curve) of EM group is about one fold larger than that of IM group ($P < 0.05$).

DISCUSSION

There are emerging PK-PD reports regarding drugs with narrow therapeutic range, large inter-individual variability, and a lag between effect and level. Sheiner *et al*[7] first suggested an effect compartment model to

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 Oct; 22 (10)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

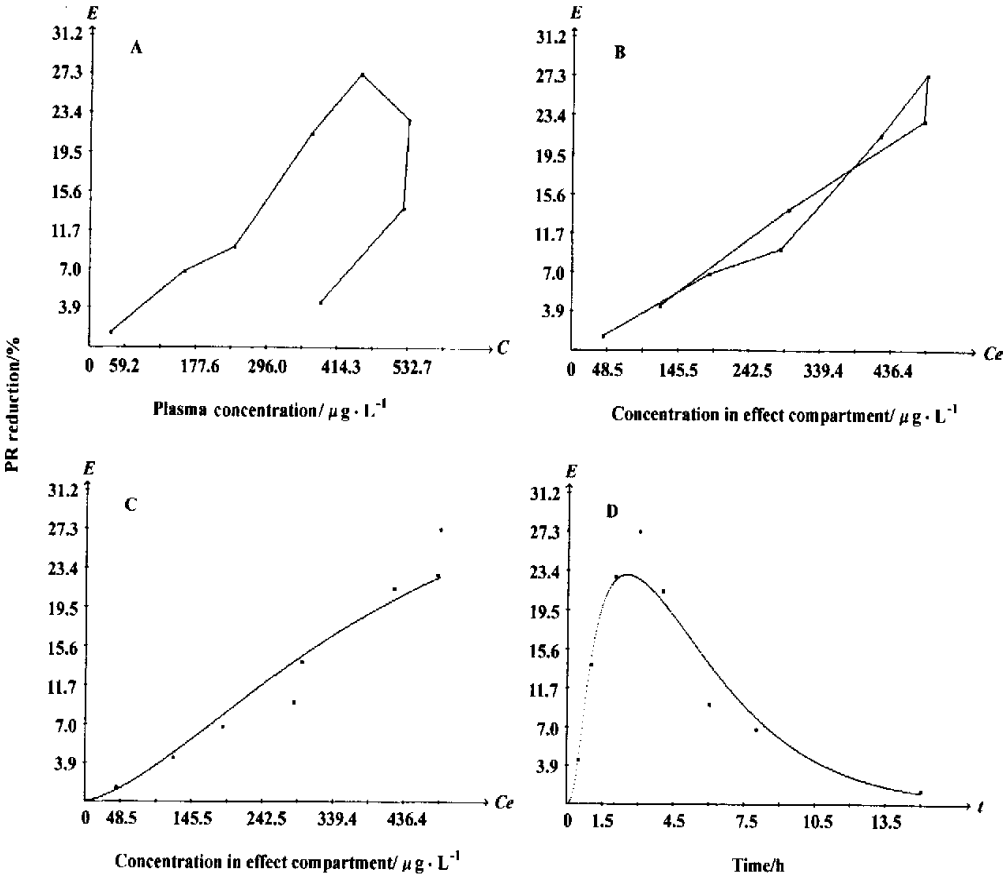

Fig 3. Propafenone average concentration versus average effect (percentage of *PR* interval prolongation) simulated with Sigmoid E_{max} model in 10 healthy subjects. A: concentration-effect curve. B: concentration-effect curve connected with central compartment. C: concentration in effect compartment versus effect. D: effect-time curve of propafenone predicted by sigmoid E_{max} model.

Tab 1. Pharmacokinetic parameters of propafenone in 10 healthy Chinese subjects after oral administration of 400 mg propafenone hydrochloride.

Parameters	1	2	3	4	5	6	7	8	9	10	$\bar{x}$	s
C_{max}/μg·L^{-1}	196.1	904.8	386.6	857.6	531.1	780.1	858.7	590.7	969.1	936.8	701	262
T_{max}/h	2.34	0.50	1.87	1.07	1.98	0.80	2.10	1.39	0.80	1.11	1.4	0.6
K_a/h^{-1}	0.62	4.73	1.06	1.89	1.18	2.41	0.90	1.60	3.13	1.40	1.9	1.2
$t_{1/2Ka}$/h	1.12	0.15	0.65	0.37	0.59	0.29	0.77	0.43	0.22	0.49	0.51	0.29
α/h^{-1}	0.31	1.31	0.25	0.50	0.18	0.90	0.22	0.24	0.71	0.85	0.55	0.38
$t_{1/2α}$/h	2.22	0.53	2.73	1.39	3.92	0.77	3.23	2.86	0.97	0.82	1.9	1.2
β/h^{-1}	0.28	0.35	0.21	0.36	0.15	0.09	0.22	0.20	0.18	0.15	0.22	0.09
$t_{1/2β}$/h	2.47	1.96	3.26	1.94	4.60	7.56	3.23	3.47	3.84	4.79	3.7	1.7
V_d/L	71.2	27.9	47.2	17.0	31.7	46.5	17.0	37.1	27.9	28.7	35	16
$AUC_{0-\infty}$/μg·h·L^{-1}	1344	2598	2672	3435	4692	5446	6269	3451	5163	5304	4037	1569
Cl/L·h^{-1}	332.3	164.3	167.2	101.0	79.5	71.0	60.7	123.7	84.0	69.2	125	82

K_a: absorption constant; α: distribution constant; β: elimination constant; $t_{1/2}$: half-life; V_d: total apparent volume; AUC: area under curve; Cl: clearance rate; C_{max}: peak concentration; T_{max}: time to reach peak concentration.

Tab 2. Pharmacodynamic parameters of propafenone as determined by percentage of PR interval prolongation after an oral dose of 400 mg propafenone hydrochloride in 10 healthy Chinese subjects.

Parameters	1	2	3	4	5	6	7	8	9	10	$\bar{x}$	s
K_{eo}	1.19	0.79	1.51	1.18	0.68	0.95	1.67	1.90	1.26	1.12	1.2	0.4
E_{max}/%	37.1	24.5	47.4	41.6	53.6	28.4	58.1	54.3	65.1	64.0	47	14
$Ce_{50}/\mu g \cdot L^{-1}$	148.4	466.8	375.3	392.5	412.4	477.2	1216	601.5	714.1	727.3	553	289
γ	2.94	4.22	2.42	3.79	1.73	2.35	1.68	1.76	1.43	0.88	2.3	1.1

K_{eo}: elimination constant in effect compartment; s: slope in linear model which approaches the value of E_{max}/EC_{50}.

Tab 3. Comparisons of pharmacokinetics of propafenone between EM and IM phenotypes of Chinese subjects. $n = 10$. $\bar{x} \pm s$. [b] $P < 0.05$ *vs* EM. IM: corrected parameters.

	α/h^{-1}	$t_{1/2\alpha}$/h	β/h^{-1}	$t_{1/2\beta}$/h	K_a/h^{-1}	$t_{1/2Ka}$/h	V_d/L	$AUC_{0-\infty}$/ $\mu g \cdot h \cdot L^{-1}$	Cl/ $L \cdot h^{-1}$	C_{max}/ $\mu g \cdot L^{-1}$	T_{max}/h
EM	0.5±0.5	2.2±1.3	0.27±0.09	2.9±1.1	1.9±1.6	0.6±0.4	39±21	2948±1230	169±99	575±304	1.6±0.8
IM	0.6±0.3	1.7±1.2	0.17±0.05	4.6±1.8	1.9±0.9	0.4±0.2	31±11	5126±1030[b]	82±25	829±151	1.2±0.5

Tab 4. Comparisons of pharmacodynamics of propafenone between EM and IM phenotypes of Chinese subjects. $n = 10$. $\bar{x} \pm s$. [b] $P < 0.05$ *vs* EM. IM: corrected parameters.

	K_{eo}/h^{-1}	E_{max}/%	$Ce_{50}/\mu g \cdot L^{-1}$	γ
EM	1.1±0.3	41±11	359±123	3.0±1.0
IM	1.4±0.4	54±15	747±281[b]	1.6±0.5[b]

relate drug level to pharmacological effect. Our previous study on metoprolol had shown that a PK-PD model could explain stereoselective differences of drug disposition and action in spontaneously hypertensive rat[8]. In present study, we found that there exists delay between Pro level and its effect in 10 subjects after administration of 400 mg of Pro hydrochloride. It suggests that the peaks of plasma level appear earlier than effect peaks, indicating the presence of effect compartment. After simulating with sigmoid model, we obtained a good relation of effect with time, which provided theoretical basis for forecasting maximum effect, the lag time between effect and level, and possible maintaining time of drug effect. There are magnificent differences in pharmacokinetics and pharmacodynamics between CYP2D6 EM and IM phenotypes. AUC of IM group is around two fold higher than that of EM group, which results in same fold increase of Ce_{50} in IM group as compared to that in EM group.

In conclusion, genetic polymorphism of CYP2D6 could not only influence pharmacokinetic of Pro, but also its pharmacological effect at the same time. The further study on PK-PD of Pro and other CYP2D6 substrates in patients will provide useful information of rational use of these agents clinically.

REFERENCES

1 Hii JT, Duff HJ, Burgess ED. Clinical pharmacokinetics of propafenone. Clin Pharmacokinet 1991; 21: 1-10.
2 Cai WM, Chen B, Cai MH, Zhang YD. CYP2D6 phenotype determines pharmacokinetic variability of propafenone enantiomers in 16 HAN Chinese subjects. Acta Pharmacol Sin 1999; 20: 720-4.
3 Lalonde RL. Pharmacodynamics. In: Evans WE, Schentag JJ, Jusko WJ, editors. Appliled pharmacokinetics-principles of therapeutic drug monitoring; 3rd ed. Vancouver, WA: Applied Therapeutics, Inc; 1992. p 4.1-4.33.
4 Cai WM, Chen B, Liu YX, Chu X. Dextromethorphan metabolic phenotyping in a Chinese population. Acta Pharmacol Sin 1997; 18: 441-4.
5 Chen B, Cai WM, Wan W. Determination of propafenone enantiomeric concentrations I human plasma by stereoselective high performance liquid chromatography. Chin Pharm J 1998; 33: 546-9.
6 Yin XX, Zhang YD, Sheng JP, Luo JP, Huang XP, Ding Y, *et al*. Simultaneous modeling of pharmacokinetics and pharmacodynamica of metoprolol in normotensive spontaneously hypertensive rats. Chin J Pharmacol Toxicol 1996; 10: 140-5.
7 Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J.

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 Oct; 22 (10)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to *d*-tubocurarine. Clin Pharmacol Ther 1979; 25: 358-71.

8 Yin XX, Zhang YD, Luo JP, Huang XP, Shen JP, Ding Y, *et al*. Pharmacokinetic-pharmacodynamic modeling of metoprolol stereoisomers in spontaneously hypertensive rat. Acta Pharmacol Sin 1997; 18: 104-8.

普罗帕酮在健康受试者中的药动-药效学结合模型研究

蔡卫民[1]，张银娣[2]，陈 冰[3]，蔡明虹[3]，
罗建平，凌树森[3]（南京医科大学临床药理研究所，[3]南京金陵医院临床药理科，南京 210029，中国）

关键词 普罗帕酮；药代动力学；模型；细胞色素 P-450 CYP2D6

目的：采用药动-药效结合模型观察普罗帕酮血浆浓度与心电图指标 PR 间期延长百分率的数量关系，并求算药效学参数. **方法**：选择健康汉族受试者 10 名，其中 CYP2D6 表型的快代谢型(EM)和中速代谢型(IM)各 5 名. 受试者口服普罗帕酮片剂 400 mg，于给药后 15 h 内抽取静脉血，并同步测定受试者 PR 间期. 普罗帕酮浓度采用高效液相色谱分析法测定. 采用 CAPP 软件对普罗帕酮血药浓度及 PR 间期延长百分率进行药动-药效结合模型计算. **结果**：10 例健康志愿者的普罗帕酮血浆浓度与效应之间存在着滞后现象. 经采用 CAPP 软件拟合数据，发现效应与浓度之间符合 Sigmoid E_{max} 模型. IM 组的 AUC ($\mu g \cdot h \cdot L^{-1}$) 明显高于 EM 组 (5126 ± 1030 *vs* 2948 ± 1230, $P < 0.05$)；相对应药效参数 Ce_{50} IM 组也比 EM 组大 ($P < 0.05$). 另外，效应曲线 S 线程度的参数 γ EM 组大于 IM 组 ($P < 0.05$). **结论**：CYP2D6 遗传多态性不但对普罗帕酮的药动学有影响，而且对其药效学参数可能也有明显的影响.

(责任编辑 吕 静)