The influence of CYP2D6 activity on the kinetics of propafenone enantiomers in Chinese subjects

W. M. Cai, B. Chen, M. H. Cai, Y. Chen & Y. D. Zhang¹

Department of Clinical Pharmacology, Jinling Hospital, and ¹the Institute of Clinical Pharmacology, Nanjing Medical University, Nanjing, China

Aims To determine role of CYP2D6 activity in the pharmacokinetics of propafenone (PPF) enantiomers in native Chinese subjects.

Methods Sixteen extensive metabolizers (EMs) and one poor metabolizer (PM), whose phenotype had been previously assessed with dextromethorphan metabolic phenotyping, were enrolled. Blood samples (0–15 h) were taken after oral administration of a single dose (400 mg) of racemic-propafenone hydrochloride. A reverse-phase h.p.l.c. method with pre-column derivatization was employed to quantitate enantiomeric concentrations of propafenone in plasma.

Results For the EM subjects, S-PPF was less rapidly metabolized and had higher peak plasma concentrations than R-PPF (413 ± 143 vs 291 ± 109 ng ml⁻¹, $P < 0.001$). The AUC was markedly higher for S-PPF than for R-PPF (2214 ± 776 vs 1639 ± 630 µg h l⁻¹, $P < 0.001$), whereas the clearance of S-PPF was significantly lower than that of R-PPF (96.0 ± 39.0 vs 138 ± 78 l h⁻¹, $P < 0.01$). There were no differences in $t_{1/2}$, and $C_{\max}$ between the two isomers ($P > 0.05$). In the one PM subject, not only did S-PPF appear to undergo less rapid metabolism than R-PPF, but the subject also showed 2–3 fold differences in $C_{\max}$, CL and AUC compared with EMs. The correlation coefficients (r_s) between dextromethorphan metabolic ratio (lg MR) and pharmacokinetic parameters ($C_{\max}$, CL and AUC) were 0.63, -0.87, 0.87 for S-PPF and 0.57, -0.73, 0.86 for R-PPF, respectively.

Conclusions Our results suggest that CYP2D6 activity contributes to the pharmacokinetic variability of propafenone enantiomers in Chinese subjects.

Keywords: propafenone, enantiomer, pharmacokinetics, CYP2D6, phenotype, Chinese

Introduction

Propafenone (PPF), a commonly used antiarrhythmic agent, is given clinically as a racemic mixture of S-PPF and R-PPF [1]. The two enantiomers are metabolized at different rates in Caucasians, with the R-PPF being eliminated faster than the S-PPF [2]. Propafenone is biotransformed mainly through cytochrome P450 2D6 (CYP2D6) to the active metabolite 5-hydroxypropafenone (5-OH PPF) and less importantly through CYP3A4 to N-desalkylpropafenone (N-desalkyl PPF). Previous work has shown that the metabolism of PPF is polymorphic and genetically determined, resulting in higher plasma drug concentrations in the 7% of Caucasians who are poor metabolizers (PMs) with respect to CYP2D6 [3]. Our recent research on dextromethorphan

metabolic phenotyping in a Chinese population has shown that Chinese extensive metabolizers (EMs) consisted of about 99% (119/120) of the Chinese population and that only one subject could be classified as a PM with respect to CYP2D6 [4]. The purpose of this study was to examine the disposition of propafenone enantiomers in 16 EMs and one PM to determine if stereoselective pharmacokinetics of propafenone occurs and whether the kinetics of propafenone enantiomers depends on CYP2D6 activity in Chinese subjects.

Methods

Subjects

Seventeen (eleven men and six women) healthy native Chinese subjects (age range, 23 to 45 years; weight range, 50 to 75 kg) were recruited from our previous study population of 120 volunteers undergoing dextromethorphan metabolic phenotyping of CYP2D6 [4]. Sixteen

Correspondence: Dr Wei-Min Cai, Department of Clinical Pharmacology, Jinling Hospital, 305 Zhong-Shan Dong Road, Nanjing 210002, P. R. of China.

Received 8 June 1998, accepted 15 January 1999.

subjects (10 men, 6 women) were classified as EMs ($\lg MR < -0.52$) and one subject (male) as a PM ($\lg MR \geq -0.52$). All subjects were healthy as assessed by the medical history, physical examination, electrocardiograms, and routine laboratory testing. All were non-smokers and drug free for at least 2 weeks before and during the study. The study was approved by the Hospital Ethics Committee. Informed consent was obtained from all subjects.

Protocol

After an overnight fast, subjects received 400 mg *rac*-propafenone hydrochloride tablets (XingYi Pharmaceutical Company, Shanghai, China, Lot No. 96100037) orally. An intravenous catheter 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 drug administration. Plasma was separated and stored at -20°C until assay.

Drug measurement and data analysis

Propafenone enantiomers were determined by a reverse-phase high performance liquid chromatography (h.p.l.c.) method established in our laboratory [5]. The limits of detection of S-PPF and R-PPF were 10 ng ml^{-1} and 13 ng ml^{-1} , respectively. The average intraday and interday CV were all below 6%, and average recovery was 102.2%.

The pharmacokinetic parameters (k , $t_{1/2}$, $C_{\max}$, $t_{\max}$) of propafenone enantiomers were obtained from a PKBP-N1 computer program with one-compartment simulation[6]. Area under the plasma concentration-time curve (AUC) was determined by the trapezoidal rule and extrapolated to infinity by calculation of C_t/k , where C_t is the last plasma concentration determined at 15 h. Apparent oral clearance (CL) was calculated as dose/AUC. Differences in the pharmacokinetics between S-PPF and R-PPF were tested by the *t*-test for paired samples. A *P* value of less than 0.05 was regarded as statistically significant. 95% Confidence intervals (95% CI) for differences in means were also calculated. The Spearman rank test was used to determine the degree of association between pharmacokinetic parameters of propafenone enantiomers and dextromethorphan metabolic ratio (MR). Data are shown as mean $\pm$ s.d.

Results

Figure 1 shows the plasma concentration-time profile of propafenone enantiomers in 16 Chinese EMs and one PM with respect to CYP2D6 after a single oral dose (400 mg) of *rac*-propafenone hydrochloride. There were

Figure 1 Plasma concentration-time profile of propafenone enantiomers among 16 Chinese EMs (a) and one PM (b) with respect to CYP2D6. $\circ$ S-PPF, Δ R-PPF.

significant differences in the stereoselective disposition among subjects between S-PPF and R-PPF. For the EM subjects, S-PPF was less rapidly metabolized and had higher peak plasma concentrations ($413 \pm 143\text{ ng ml}^{-1}$) than R-PPF ($291 \pm 109\text{ ng ml}^{-1}$) (difference: $122 \pm 61\text{ ng ml}^{-1}$, 95% CI: $89 \sim 154\text{ ng ml}^{-1}$, $P < 0.001$). The AUC was markedly higher for S-PPF ($2214 \pm 776\text{ }\mu\text{g l}^{-1}\text{ h}$) than for R-PPF ($1639 \pm 630\text{ }\mu\text{g l}^{-1}\text{ h}$) (difference: $575 \pm 273\text{ }\mu\text{g l}^{-1}\text{ h}$, 95% CI: $430 \sim 720\text{ }\mu\text{g l}^{-1}\text{ h}$, $P < 0.001$), whereas, the clearance of S-PPF ($96.0 \pm 39.0\text{ l h}^{-1}$) was significantly lower than that of R-PPF ($138 \pm 78\text{ l h}^{-1}$) (difference: $41.9 \pm 47.6\text{ l h}^{-1}$, 95% CI: $16.5 \sim 67.3\text{ l h}^{-1}$, $P < 0.01$). There were no differences in $t_{1/2}$, and $C_{\max}$ between the two isomers ($P > 0.05$). In the one PM subject, not only did S-PPF appear to be less rapidly metabolized than R-PPF, but the subject also showed 2~3 fold differences in $C_{\max}$, CL and AUC compared with EMs. The correlation coefficients (r_s) between the dextromethorphan metabolic ratio ($\lg MR$) and the pharmacokinetic parameters $C_{\max}$, CL and AUC, were 0.63, -0.87 , 0.87 for S-PPF and 0.57, -0.73 , 0.86 for R-PPF, respectively (Figure 2). Intake of propafenone was associated with dizziness in

Figure 2 Correlation between the dextromethorphan metabolic ratio and the $C_{\max}$, oral CL and AUC of S-propafenone (a) and R-propafenone (b) in 16 Chinese EMs (open circles) and one PM (solid circles).

five subjects (four EMs and one PM). The PM subject also experienced gastrointestinal symptoms (nausea and gastric irritation) and dizziness which persisted for 10 h.

Discussion

Propafenone, a drug with a narrow therapeutic range, undergoes stereoselective disposition and is subject to a genetic polymorphism in its metabolism, which is mediated by CYP2D6 [7]. For Chinese, especially those living in mainland China, studies on the enantiomeric disposition of propafenone and its relationship to CYP2D6 activity are limited. Kuang *et al.* studied propafenone pharmacokinetics in eight Chinese EM and one PM [8]. Although substantial variability in the pharmacokinetic parameters ($t_{1/2}$, AUC, CL) were found, they were not correlated with CYP2D6 activity. Likewise, Zhong *et al.*

investigated the stereoselective pharmacokinetics of propafenone enantiomers in 10 healthy Chinese subjects [9], but did not relate them to CYP2D6 activity.

The present investigation is the first to describe the role of genetically determined CYP2D6 activity in the disposition of propafenone enantiomers in Chinese subjects. We found R-propafenone was preferentially eliminated in both the EMs and the one PM subjects. The latter achieved a 2~3 fold higher plasma drug concentrations of both enantiomers compared to EMs as a result of lower clearance. Our results are similar to those in Caucasians [7]. Furthermore, there was a significant correlation between the pharmacokinetics of propafenone enantiomers and the dextromethorphan MR. Thus, our study suggests that CYP2D6 activity contributes to the variability in pharmacokinetics of propafenone in Chinese subjects.

This study was supported by the Army Medical Research Foundation of PLA, China (grant No. 96M023) and by the National Research Foundation of Overseas Scholar (grant No. 9701). We thank Dr Mary H. H. Enson, the associate professor of Faculty of Pharmaceutical Sciences, University of British Columbia, Canada, for her invaluable help in the preparation of our manuscript.

References

- 1 Hii JTY, Duff HJ, Burgess ED. Clinical pharmacokinetics of propafenone. *Clin Pharmacokinet* 1991; **21**: 1–10.
- 2 Volz M, Mitrovic V, Schlepper M. Steady-state plasma concentrations of propafenone-chirality and metabolism. *Int J Clin Pharmacol Ther* 1994; **32**: 370–375.
- 3 Siddoway LA, Thompson KA, McAllister CB, et al. Polymorphism of propafenone metabolism and disposition in man: Clinical pharmacokinetic consequences. *Circulation* 1987; **75**: 785–791.
- 4 Cai WM, Chen B, Liu YX, Chu X. Dextromethorphan metabolic phenotyping in a Chinese population. *Acta Pharmacol Sin* 1997; **18**: 441–444.
- 5 Chen B, Cai WM, Wan W. Determination of propafenone enantiomeric concentrations in human plasma by stereoselective HPLC. *Chin Pharm J* 1998; **33**: 546–549.
- 6 Yang YC, Chen G, Yuan L. A non-linear method and its program for calculating pharmacokinetic parameters. *Acta Pharmacol Sin* 1983; **4**: 217–220.
- 7 Kromer HK, Funck-Brentano C, Silberstein DJ, et al. Stereoselective disposition and pharmacologic activity of propafenone enantiomers. *Circulation* 1989; **79**: 1068–1076.
- 8 Kuang TY, Lou YC, Tao P. Pharmacokinetics of propafenone and its relationship with debrisoquin and mephenytoin metabolism polymorphisms in healthy Chinese volunteers. *Chin J Pharmacol Toxicol* 1994; **8**: 13–18.
- 9 Zhong DF, Wang YQ, Wang AM. Stereoselective pharmacokinetic studies on the propafenone enantiomers. *Chin J Clin Pharmacol* 1997; **13**: 82–87.