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Sex differences in pharmacokinetics of oral propranolol in healthy Chinese volunteers[1]

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AIM: To determine if the gender-based dimorphism of the distribution and metabolism of oral propranolol (Pro) exists in the healthy Chinese volunteers. METHODS: Twelve subjects (6 M and 6 F) were given an 80 mg single oral dose of Pro. Plasma Pro levels were determined by HPLC with fluorescence detector and the pharmacokinetic parameters were calculated by using the MCPKP program. **RESULTS**: AUC and C_{max} in females were about 74 % and 99 % higher than those in males ($P<0.05$), whereas oral clearance and apparent distribution volume were 109 % and 120 % lower in females than in males ($P<0.05$), respectively. The $T_{\frac{1}{2}}$ tended to be longer in females ($P>0.05$). No differences in any other kinetic parameters were found between the sexes. **CONCLUSION**: The higher oral bioavailability (AUC and C_{max}) of Pro in Chinese women is in part caused by their lower oral clearance and volume of distribution.

KEY WORDS propranolol; oral administration; pharmacokinetics; sex characteristics

Propranolol (Pro) is highly extracted and nearly completely eliminated by hepatic metabolism during first-pass. The factors affecting Pro disposition in humans are mainly gender, race, and genetic background[1,2], in which gender is the most important biologic determinant[1]. Sex-dependent differences were found in the partial metabolic clearance (Cl_m) and total clearance (Cl_o) of oral Pro but not in the volume of distribution (V_d), elimination half-life ($T_{\frac{1}{2}}$), systemic clearance (Cl_s), plasma protein binding (PPB), and bioavailability (fraction, F) of iv Pro in American white subjects[3]. Contrary to the above findings, gender differences in the Cl_s and apparent V_d of iv Pro were observed in healthy Chinese subjects[4], but the sex-differentiated disposition of oral Pro in Chinese was not reported. This is an important consideration, because the racial differences exist in the Pro disposition between the Chinese and American whites, especially after oral administration[5]. This study was to determine if gender-related dimorphism of distribution and metabolism of oral Pro really occurred in the healthy Chinese volunteers.

SUBJECTS AND METHODS

Subjects Twelve nonsmoking young Chinese volunteers (6 M and 6 F), aged 27±6 (range 20—36) a and weighing 52±6 (range 42—60) kg, were considered healthy, as judged by medical history, physical examination, and routine laboratory screening. None of them had taken any drugs, including oral contraceptive steroids and alcohol, for at least 2 wk prior to the study. Informed consent was obtained from each subject.

Study protocol Each subject was given a single dose Pro (80 mg *po*) with 100 mL water at 8:00 after an overnight fast. Breakfast was withheld for post-dose 3 h. A venous blood sample was drawn in heparinized tubes at 0, 0.5, 1, 2, 3, 5, 8, 12, and 24 h after medication and the plasma was frozen at −20 C until analysis.

Drug assay Plasma Pro levels were measured by

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HPLC with fluorescence detection[6]. The coefficients of variation of the assay for spiked plasma were 4 %—7 %. The relative recoveries were 98 %—101 %. The lower limit of detection was ca 1 $\mu g\ L^{-1}$.

Pharmacokinetic analysis Data were analyzed by the MCPKP program[7]. The Cl_o and apparent V_d were calculated from the following equations: Cl_o = dose/AUC, $V_d = Cl_o/K_e$. Cl_o and V_d were normalized for value/kg body weight. The parameters were compared by *t* test.

RESULTS

Plasma Pro levels were lower ($P<0.05$) in the males than those in the females at 1, 2, 3 and 5 h after oral dose, but the subsequent level differences were not obvious between the 2 groups (Fig 1).

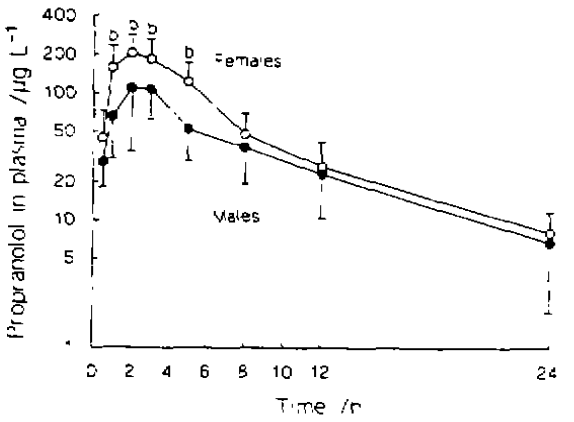

Fig 1. Time course of Pro concentrations in plasma in 6 females and 6 males after *po* 80 mg.
$^bP<0.05$ *vs* males.

Pro peak concentrations (C_{max}) at post-dose 2 h were about 99 % higher in the females ($P<0.05$). The AUC in females was about 74 % higher than that in males ($P<0.05$), whereas the Cl_o and V_d were 109 % and 120 % lower in females than in males ($P<0.05$), respectively. The $T_{\frac{1}{2}}$ seemed to be longer in females ($P>0.05$). No differences in other kinetic parameters were found between the sexes (Tab 1).

Tab 1. Sex differences in pharmacokinetic parameters of oral propranolol in Chinese subjects.
$n=6$, $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$ *vs* females.

Parameters	Males	Females
K_a/h^{-1}	1.3 ± 0.6^a	1.4 ± 0.5
K_e/h^{-1}	0.2 ± 0.1^a	0.2 ± 0.1
$T_{\frac{1}{2}a}/h$	0.7 ± 0.4^a	0.6 ± 0.3
$T_{\frac{1}{2}}/h$	4.1 ± 1.9^a	6.1 ± 4.8
T_{max}/h	2.3 ± 0.5^a	2.0 ± 0.5
$C_{max}/\mu g\ L^{-1}$	103 ± 45^b	205 ± 83
$AUC/\mu g\ h\ L^{-1}$	796 ± 315^b	$1\,384\pm532$
$Cl_o/L\ h^{-1}\ kg^{-1}$	2.3 ± 1.1^b	1.1 ± 0.4
$V_d/L\ kg^{-1}$	11.3 ± 5.7^b	5.0 ± 2.0

DISCUSSION

To assess the effects of gender on the distribution and elimination of a drug, most of the *in vivo* studies are accomplished by determining the concentration-time profile of the drug and basing their conclusions on some kinetic parameter estimates (*eg*, Cl_o, V_d, and $T_{\frac{1}{2}}$)[8,9]. The present study demonstrated that Chinese females exhibited lower Cl_o and V_d in Pro disposition. Walle's previous study also showed that sexual dimorphism of oral Pro disposition existed in the American whites[3], mainly attributing to the lower Cl_o in females than in males. In addition, the lower V_d of oral Pro in Chinese females was supported by the sexually dimorphic V_d of iv Pro in Chinese[4], but not in American whites[3]. The gender-based difference of Pro Cl_o in Chinese (109 %) was larger than that in American whites (63 %)[3]. Accordingly, this study suggests that gender-related dimorphism of Pro distribution and metabolism in Chinese differ from those in American whites. The higher oral *F* (AUC and C_{max}) of Pro in Chinese females is in part caused by their lower oral clearance and volume of distribution. The exact interpretation of these phenomena

must await more experimental evidences. Further work is required to determine if gender-differentiated response to Pro also exists in humans.

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口服普萘洛尔在健康中国人药物动力学的性别差异

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目的：确定口服普萘洛尔(Pro)的体内分布与代谢是否在健康中国人中存在性别二态性. **方法**：12名健康志愿者(6男，6女)口服单剂量 Pro 80 mg，其血浆 Pro 浓度用 HPLC 荧光法检测，药物动力学参数用 MCPKP 软件计算. **结果**：女性的 AUC 和 C_{max} 分别比男性高 74 % 和 99 %，相反，Cl_o 和 V_d 却分别比男性低 109 %和120 %. 女性 $T_{\frac{1}{2}}$ 较长，但和男性比无显著差异，其他药物动力学参数未发现明显性别差异. **结论**：中国女性比男性有一个较高的 Pro 口服生物利用度，部分归因于她们在服药后对 Pro 的整体清除率较低和表观分布容积较小.

关键词 普萘洛尔；口服给药；药物动力学；性别特征

药代动力学