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Pharmacokinetics of sustained-release tablets of metoprolol in Chinese

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ABSTRACT Single and repeated oral doses pharmacokinetic studies of metoprolol sustained-release tablets (Sino-Swed Pharmaceutical Co Ltd) were performed on 12 Chinese healthy subjects in an open randomized crossover manner, using metoprolol tablets from Sweden Astra Insternational Pharmaceutical Co Ltd as control. Drug concentrations in plasma were assayed by gas chromatography-electron-capture detector method. The percent of drug absorbed *in vivo* at 1, 2, 4, 6, 8 h correlated well with the amount of drug released *in vitro* at corresponding time ($P>0.05$). Pharmacokinetic parameters in Chinese after metoprolol tablets were comparable to the reported data in foreigners.

KEY WORDS metoprolol; pharmacokinetics; delayed-action preparations

Metoprolol (Met) is a selective β_1-adrenoceptor antagonist and its effectiveness in treatment of hypertension and angina pectoris is well documented[1]. Being completely absorbed from the small intestine, it has a relatively short half life (2－6 h) and the degree of β_1-blockade correlates well with the plasma concentration. Several sustained-release formulations have been developed, such as Met floating tablet[2], Betaloc Durules, Met OROS system and Met CR/ZOK[3]. Recently, Betaloc Durules was introduced into China and produced in Sino-Swed Parmaceutical Co Ltd (SSPC).

This paper investigated the pharmacokinetic behaviors of the Met sustained-release tablets in Chinese healthy volunteers, so as to supply a pharmacokinetic basis for the clinical use in China.

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MATERIALS AND METHODS

Drugs and instrument Met sustained-release tablet A (lot 900508c, Sino-Swed Pharmaceutical Co Ltd, China) and B (lot MI－15, Astra International Pharmaceutical Co Ltd, Sweden). Each tablet contained 100 mg Met. The model 1001 gas chromatography was equipped with an electron-capture detector.

Subjects Twelve healthy Chinese volunteers aged $25\pm s$ 4 a and weighed 64 ± 6 kg. All volunteers gave their written consent after informed of the nature of the trial and underwent a physical examination before the study. There were no abnormal findings in their liver and kidney functions in particular.

Protocol The study protocol was reviewed and approved by the Pharmaceutical Affairs Committee of Jinling Hospital.

In the single dose study, volunteers entered the study in an open, randomized crossover study design. After 12 h of overnight fast, single dose of 100 mg Met sustained-release tablet either A or B was given to each volunteer. Blood samples (4 ml) were taken before medication and at the following time periods after dosing: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h. The blood samples were collected in heparinized tubes and centrifuged at 18－20℃. Plasma was stored at －20℃ until assay. Each study was followed by a washout period of 1 wk.

The repeated-dose study was a continuation of the single-dose experiment. After all the samples mentioned above had been taken, the subjects started to take the tablets every 24 h up to 6 doses. Blood was sampled at 72, 75, 96, 99, 120, 123, and 144 h in the steady state.

Assays of metoprolol Met in plasma was determined by gas chromatography plus ECD detecter[4]. The linear range was 10－1500 ng · ml^{-1}, and mean recovery from plasma was $97.3\pm2.7\%$. The coefficients of variation of day-to-day and within-day were less than 8% and 7%, respectively.

Correlation *in vivo vs in vitro* The percent of Met absorbed *in vivo* was calculated by the Wagner-Nelson method. The data of dissolution rate were obtained by the basket method according to the Chinese pharmacopoeia (1990). The *in vivo vs in vitro* correlation was based on the least square regression method.

Pharmacokinetic analysis The model-independent plasma parameters were: maximal plasma concentration (C_{max}); time to C_{max} (T_{max}); elimination half-life ($T_{\frac{1}{2}}$); area under the plasma concentration-time curve ($AUC_{0-\infty}$) using the trapezoidal rule; and the ratio between peak and trough concentrations in the steady state.

Comparison of bioavailability The relative bioavailability was estimated by the mean value of the ratios of $AUC_{0-\infty}$ for 12 subjects. Bioequivalence between the 2 tablet forms was assessed by determination of the confidence limits of the mean A:B ratios of $AUC_{0-\infty}$, T_{max}, C_{max}, lag time, and $T_{\frac{1}{2}}$[5].

RESULTS

After curve-fitting, it was found that a linear relationship existed not between f (fraction of drug absorbed *in vivo*) and a (amount of drug dissolved *in vitro*), but between the square of f (f^2) and a, the correlation equation was $f^2 = -5538.23 + 183.56\,a$ ($r = 0.98$, $P < 0.05$). So the *in vivo vs in vitro* correlation curve was linearized by curve describing of f^2 *vs* a instead of f *vs* a (Fig 1).

The mean Met concentrations in plasma after a single *po* dose of 100 mg of tablet A and B were in good agreement with each other (Tab 1), and the mean $AUC_{0-\infty}$ were 1910±680 and 1916±899 h·ng·ml^{-1} for tablet A and B, respectively.

Tab 1. Metoprolol (Met) concentrations in plasma (ng·ml^{-1}) after a single *po* dose of 100 mg of tablet A (SSPC, China) and B (Astra, Sweden) in 12 healthy Chinese. $\bar{x}\pm s$, $^*P>0.05$.

Time/h	Tablet A	Tablet B
0.5	23±8	26±8*
1.0	81±24	87±26*
1.5	119±45	122±40*
2.0	131±42	132±40*
3.0	148±47	151±40*
4.0	141±44	147±44*
6.0	106±38	106±43*
8.0	88±39	89±44*
12.0	56±31	58±38*
24.0	20±11	21±13*

The mean plasma concentration-time curves of tablet A and B in the steady state were similar (Fig 2), and the mean C_{max}, C_{min} and ratios between peak and trough concentra-

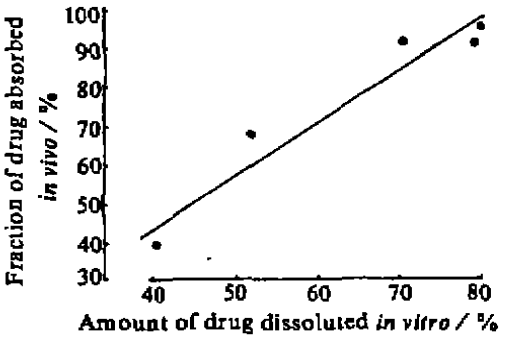

Fig 1. Correlation between *in vivo* absorption and *in vitro* dissolution of Met sustained-release tablet A (SSPC, China).

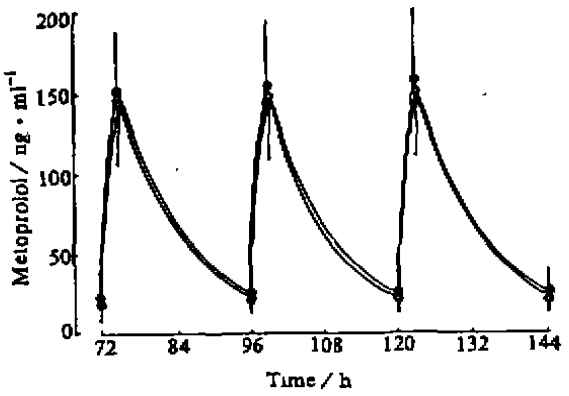

Fig 2. Met concentrations in plasma after repeated *po* doses of 100 mg Met sustained-release tablet A (●) and B (○), n = 12 men.

tions in the steady state were calculated (Tab 2), no significant difference could be detected ($P>0.05$)

Tab 2. C_{max}, C_{min}, and R (ratio between C_{max} and C_{min}) of tablet A, B ($n=12$), and reported[3] ($n=10$). $\bar{x}\pm s$, $^*P>0.05$ *vs* reported.

	Tablet A	Tablet B	Reported
C_{max} (ng·ml^{-1})	153±47*	149±43*	177±120
C_{min} (ng·ml^{-1})	21±11*	20±13*	29±49
R	6.39	7.11	6.25

The confidence limits of the mean A:B ratios of $AUC_{0-\infty}$, T_{max}, C_{max}, lag time, and $T_{\frac{1}{2}}$ were computed by determining the conventional $1-\alpha/2$ (95%) confidence limits of the difference between the means, in each case dividing each limit by the mean value for B and adding this quotient to 1. Tab 3 shows 95% asymmetrical confidence limits for the percentage A:B ratios of means $AUC_{0-\infty}$, T_{max}, C_{max}, lag time, and $T_{\frac{1}{2}}$.

Tab 3. Bioequivalence parameters of tablet A and B. $n=12$, $\bar{x}\pm s$.

Parameter	Tablet A	Tablet B	95% Confidence limits
$AUC_{0-\infty}$/ h·ng·ml^{-1}	1910±680	1916±899	84.8～113.9
C_{max}/ ng·ml^{-1}	149±47	155±43	96.9～102.1
T_{max}/h	3.25±0.45	3.33±0.49	87.7～107.5
Lag time/h	0.33±0.10	0.35±0.08	85.7～108.6
$T_{\frac{1}{2}}$/h	5.1±1.5	4.9±1.6	88.8～115.3

DISCUSSION

The behaviors of Met sustained-tablet *in vivo* correlated closely with the behaviors *in vitro* ($P<0.05$). The mean $AUC_{0-\infty}$ in Chinese was slightly lower than the reported data of 2341±2449 h·ng·ml^{-1} in foreigners[3], but no significant difference could be detected ($P>0.05$). The mean C_{max}, C_{min}, and ratios between C_{max} and C_{min} in the steady state in Chinese were comparable to the corresponding reported data in foreigners[3]. These confidence limits for the tablet A : tablet B ratios of mean bioequivalence parameters were narrow, well within the acceptable limits of bioequivalence (80—120%), and encompassed the ideal relative bioavailability of 100%.

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美托洛尔缓释片剂在中国人体内的药物动力学

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摘要 12名中国健康志愿者随机交叉单剂量及多剂量口服100 mg美托洛尔缓释片剂(中国华瑞制药有限公司)后，利用气相色谱—电子捕获法测定血浆中药物浓度，美托洛尔片剂(瑞典Astra公司)为对照制剂。药物在1，2，4，6，8 h的体内吸收%与相应时间体外溶出量呈直线相关($P<0.05$)。服用该片剂后，中国人体内的药动学参数与所报道的外国人体内相类似。

关键词 美托洛尔；药物动力学；迟效制剂

药代动力学