BIBLID: ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1996 Sep; 17 (5): 411-414

Diltiazem concentrations in plasma *vs* PR intervals on electrocardiogram in 8 men

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KEY WORDS diltiazem; pharmacokinetics; electrocardiography; drug tolerance

AIM: To develop an acute tolerant model in describing relationship between diltiazem (Dil) concentrations in plasma and PR intervals on ECG in men. **METHOD:** Both plasma concentrations of Dil and changes of ECG were simultaneously determined after *po* Dil 90 mg in 8 men. **RESULTS:** A two-compartmental pharmacokinetic model with first-order input gave a good fitting for the plasma concentration of Dil. Corresponding pharmacokinetic parameters were estimated: $t_{\frac{1}{2}\beta}$, 5.9±1.0 h; *MRT*, 15.9±1.0 h; t_0, 0.38±0.07 h; t_{max}, 2.7±0.4 h, and C_{max}, 161±60 μg·L^{-1}. The good fittings for plasma concentration-effect data were obtained with tolerant model $E = S \times C/(1 + T/T_{50})$. The pharmacodynamic parameters were given as follows: S, 829±293 s·g^{-1}·L; K_{t0}, 0.037±0.024 h^{-1} and T_{50}, 10±4 μg·L^{-1}. **CONCLUSION:** Relationship between Dil concentrations in plasma and PR interval changes in men after *po* 90 mg was described using an acute tolerant model.

Diltiazem (Dil) is a calcium channel blocker. It was widely used in therapy of cardiovascular disorders. The relationship between pharmacokinetics and pharmacodynamics showed there was a positive relationship between plasma concentration and PR interval change, but when the points on plots were connected in chronologic order, there was a prominent clock-wise hysteresis[1]. This indicated that there existed a form of acute tolerance.

The goal of this investigation was to develop an acute tolerant model in describing relationship between PR interval changes and plasma concentrations of Dil after *po*.

Received 1994-09-09 Accepted 1996-04-23

MATERIALS AND METHODS

Subjects Eight healthy male volunteers (aged, 22±*s* 1 a and weighed 60 ± *s* 5 kg) entered the study. The volunteers abstained from any other drugs, including alcohol, for 2 wk before the study and during the study day.

Experimental protocol The subjects, fasted overnight, were given *po* three 30-mg tablets of Dil (Shanghai Yan-an Pharmaceutical Factory) with 200 mL of water. Collections of 5 mL blood samples were made in heparinized glass tubes, at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after *po*. Plasma 2 mL was obtained and plasma Dil concentrations were assayed by HPLC method[2] using a mobile phase of $NH_4H_2PO_4$ 0.05 mol·L^{-1}, acetonitrile, methanol, and triethylamine (50:25:25:0.25).

ECG was simultaneously recorded before drug administration and postdose: 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h. The PR interval was measured.

Pharmacokinetic-pharmacodynamic model The model developed by Porchet *et al* (Fig 1) consisted of three parts[3].

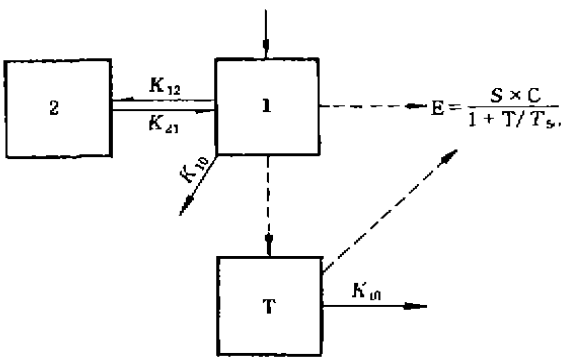

Fig 1. Pharmacokinetic and pharmacodynamic model for Dil tolerance. K_{ij} = intercompartmental transfer and elimination rate constants, C = plasma concentration of Dil, T = concentration of hypothetical antagonist, T_{50} = concentration of hypethetical antagonist resulting in 50 % inhibition of effect, S = slope of linear relation between effect and concentration, E = effect, and K_{t0} = elimination rate constant of antagonist.

Pharmacokinetic model was a classical linear two-compartmental model with first-order input.

Link model[3] was a "tolerance" compartmental

model, which linked C to E, to the negative aspects through a hypothetical antagonist (T). The model for tolerance introduced 2 parameters: the first-order rate constant (K_{t0}) governing the rate of onset and decline of tolerance after exposure to C and the concentration of hypothetical antagonist (T_{50}) resulting in 50 % inhibition of effect.

The pharmacodynamic model was:

$$E = S \times C/(1 + T/T_{50}) \quad (1)$$

where E was PR interval change, ie, measured PR interval-baseline PR interval, C was plasma concentration of Dil, T was concentration of hypothetical antagonist and S was the slope governing the linear relationship of E to C.

The concentration-time data were fitted by one- and two-compartmental pharmacokinetic model with first-order input using PKBP-N1 program[4], respectively.

The relationship of plasma concentration of Dil and PR interval change was described using Eq 1. The parameters of pharmacodynamics K_{t0}, S, and T_{50} were estimated using least-square nonlinear regression[4]. The pharmacokinetic parameters estimated were used to fit the pharmacodynamic model to the corresponding effect data. The goodness of fit was assessed by the coefficient of determination r^2 [5], and AIC[6].

RESULTS AND DISCUSSION

Pharmacokinetics The mean plasma concentration-time profile for Dil in 8 men was shown in Fig 2.

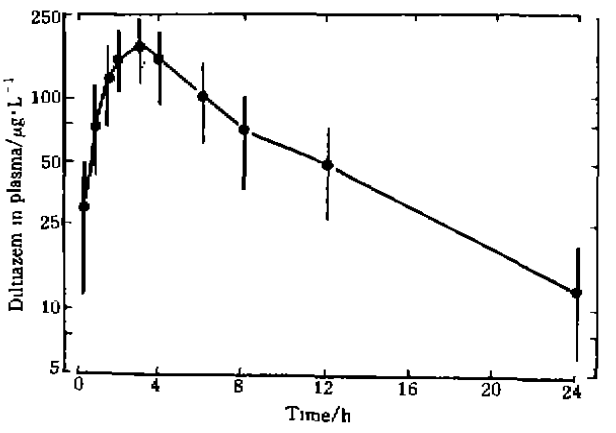

Fig 2. Dil in plasma of 8 men after *po* Dil 90 mg ($\bar{x} \pm s$).

A two-compartmental model provided a better fit than a one-compartment model did, by the objective measure of the AIC. The pharmacokinetic parameters for two-compartment model were estimated and listed in Tab 1.

Tab 1. Pharmacokinetic and pharmacodynamic parameters for Dil after *po* 90 mg ($n = 8$).

Parameters	$\bar{x} \pm s$
A, $\mu g \cdot L^{-1}$	219 ± 67
B, $\mu g \cdot L^{-1}$	125 ± 57
C_{max}, $\mu g \cdot L^{-1}$	161 ± 60
t_{max}^{a}, h	2.7 ± 0.4
t_0, h	0.38 ± 0.07
$t_{\frac{1}{2}\alpha}$, h	2.7 ± 0.6
$t_{\frac{1}{2}\beta}$, h	5.9 ± 1.0
$t_{\frac{1}{2}ka}$, h	0.87 ± 0.15
MRT, h	15.9 ± 1.0
Cl/F, $L \cdot h^{-1}$	64 ± 31
AUC, $\mu g \cdot h \cdot L^{-1}$	1 658 ± 684
S, $s \cdot g^{-1} \cdot L$	827 ± 293
K_{t0}, h^{-1}	0.037 ± 0.024
T_{50}, $\mu g \cdot L^{-1}$	10 ± 4
t_{max}^{b}, h	1.64 ± 0.21
E_{max}, ms	82 ± 21

a, time of peak concentration; b, time of peak effect

The peak concentration of Dil ranged from 63 to 239 $\mu g \cdot L^{-1}$ (161 ± 60 $\mu g \cdot L^{-1}$) and occurred between 2.33 and 3.38 h (2.7 ± 0.4 h) after the dose. The $t_{\frac{1}{2}\beta}$ and the apparent oral clearance (Cl/F) were 5.9 ± 1.0 h and 64 ± 31 $L \cdot h^{-1}$, respectively. Our mean estimate of the $t_{\frac{1}{2}}$ of Dil (5.9 h) was in accordance with that[1], but higher than that of Xiao's[7]. The mean value of t_{max} 2.7 h was consistent with that[7]. The mean value of Cl/F was lower than that[1]. The mean lag time in the 8 men was 0.4 h.

Pharmacodynamics When both the changes in PR interval and the plasma concentrations were plotted against time, it was found that the peak concentrations were behind the peak effects. Furthermore, when the points on plots were connected in chronologic order, there was a prominent clockwise hysteresis loop in the 8 men (Fig 3).

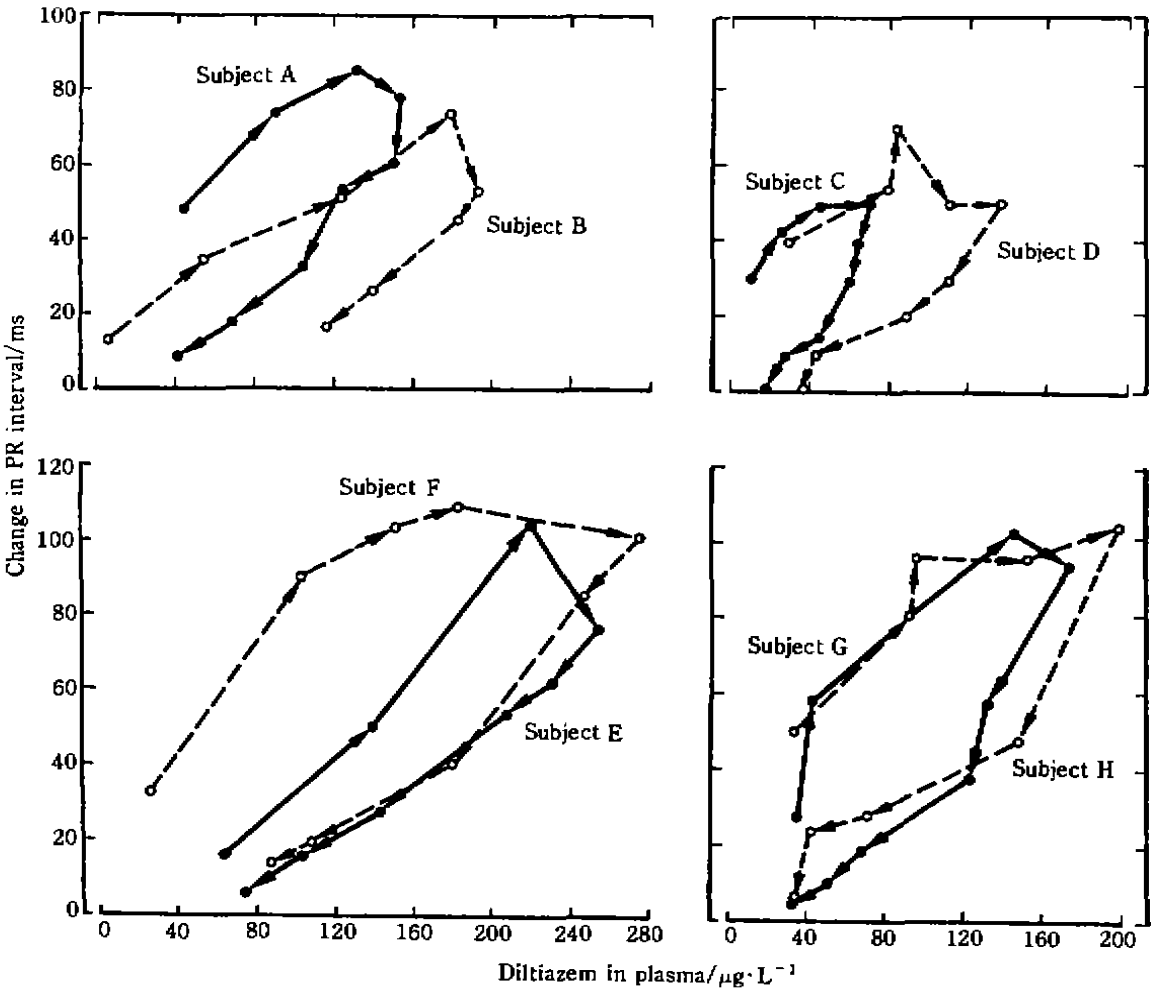

Fig 3. Change in PR interval *vs* Dil concentration in 8 men. Direction of arrows indicates chronologic order of the concentrations.

Because clockwise hysteresis may imply some form of acute tolerance[8], we fitted our Dil concentration-effect data to the pharmacodynamic model of tolerance (Fig 1). The good fittings were found in all men, with the values of $r^2 > 0.95$.

The changes of PR and plasma concentration of Dil, as well as the concentrations of the hypothetical antagonist for subject A were shown in Fig 4. The measured effects were in accordance with those predicated ($r^2 = 0.989$).

The estimated values of K_{t0}, 0.037 ± 0.024 h^{-1}, indicated that the $t\frac{1}{2}$ of development and regression of tolerance to Dil was approximately 19 h. That was to say, $4-5$ $t\frac{1}{2}$ (about 4 d) after a dose, nearly full sensitivity should have been regained. The estimated value of T_{50}, 10 ± 4 $\mu g \cdot L^{-1}$, indicated that the mean concentration of hypothetical antagonist resulting in 50 % inhibition of effect was 10 $\mu g \cdot L^{-1}$. The estimated value of S, 827 ± 293 $s \cdot g^{-1} \cdot L$, showed the sensitivity of subjects to Dil in the absence of any tolerance.

Our experiment demonstrated a rapid acute development of tolerance to prolongation in PR interval of Dil, evidenced by clockwise hysteresis when change in PR interval was plotted against the

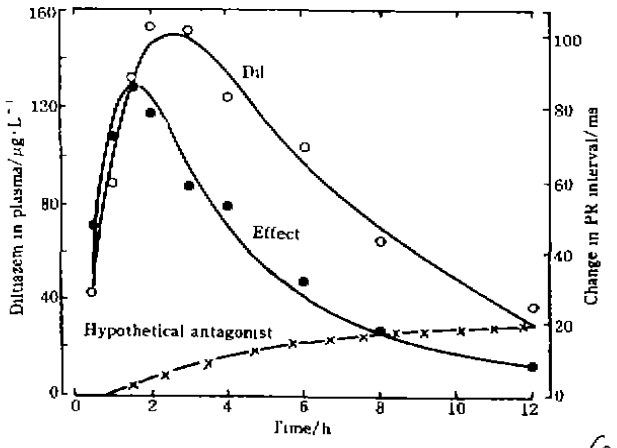

Fig 4. Dil concentration, hypothetical antagonist concentration, and change in PR interval *vs* time for subject A after *po* Dil 90 mg.

concentration of Dil. This indicated a decreasing effect with time for the same concentration of Dil. The result was consistent with that reported by Boyd *et al*[1]. The acute tolerance model provided a good fit of plasma concentration-effect data of Dil after *po* 90 mg.

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G11-414

地尔硫䓬在 8 名男子血浆中浓度与 PR 间隔关系

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关键词 地尔硫䓬；药物动力学；心电图；药物耐受

目的：建立描述血浆中地尔硫䓬(Dil)浓度与 PR 间隔关系的耐受模型。**方法**：8 名男性受试者口服Dil 90 mg 后，同时测定血浆浓度和 ECG。**结果**：口服 Dil 后，血药浓度－时间数据符合二房室模型。相应药动学参数：$t_{\frac{1}{2}\beta}$，*MRT* 和 t_0 分别为 5.9±1.0，15.9±1.0 和 0.38±0.07 h；t_{max}和 C_{max}分别为 2.7±0.4 h 和 161±60 μg·L^{-1}。耐受模型 $E=S\times C/(1+T/T_{50})$能很好拟合浓度 C 与效应 E 间关系。药效学参数：*S*，K_{t0}和 T_{50}分别为 827±293 s·g^{-1}·L，0.037±0.024 h^{-1}和 10±4 μg·L^{-1}。**结论**：用耐受模型描述口服给药后血浆中 Dil 浓度与 PR 间隔间的关系。

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