钾通道开放剂 BPDZ79 血管扩张

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新钾通道开放剂 BPDZ 79 对离体主动脉的扩血管作用[1]

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关键词 BPDZ 79; 钾通道; 胸主动脉; 血管扩张; 血管内皮; 二氮嗪; 氯化钾; 格列本脲; 铷放射性同位素

目的: 本研究旨在比较一种新钾通道开放剂 BPDZ 79 和二氮嗪对血管平滑肌的影响. **方法**: 实验在离体大鼠主动脉上进行, 第一步实验将一去内皮的主动脉分四段安置于四个浴槽内, 一段用 KCl 80 mmol·L^{-1} 预收缩, 另三段用 KCl 30 mmol·L^{-1} 预收缩, 分别用格列本脲 0, 1, 10 μmol·L^{-1} 作培养. 在此条件下, 分别测 BPDZ 79 和二氮嗪引起的扩张. 第二步实验在有或无格列本脲存在的情况下, 分别测 BPDZ 79 和二氮嗪对 ^{86}Rb 流出量的影响. **结果**: BPDZ 79 和二氮嗪在 KCl 30 mmol·L^{-1} 预收缩的血管上引起剂量相关的扩张, 而在高钾情况下 (KCl 80 mmol·L^{-1}), 却不能引起舒张. 在 ATP 敏感性钾通道抑制剂格列本脲存在的情况下, BPDZ 79 和二氮嗪引起的舒张明显减弱. **结论**: BPDZ 79 是一种新的二氮嗪的衍生物, 通过打开 ATP 敏感性钾通道而引起血管扩张.

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Pharmacokinetic-pharmacodynamic modeling of metoprolol stereoisomers in spontaneously hypertensive rat[1]

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KEY WORDS metoprolol; stereoisomers; pharmacokinetics; pharmacodynamics; inbred SHR rats

AIM: To study the combined pharmacokinetic-pharmacodynamic (PK-PD) model of metoprolol stereoisomers, and compare their inhibitory effects on cardiovascular system in the spontaneously hypertensive rats (SHR). **METHODS**: The drug concentration in plasma was measured by the reversed phase HPLC and the drug effects were recorded by polygraph. The pharmacokinetic parameters and the PK-PD model parameters were calculated. **RESULTS**: The plasma concentration-time profiles were adequately described by two-compartment model. Differences of V_d between (+)-Met and (−)-Met were found. The relationships between effects and concentration of effect compartment were represented by the sigmoid-E_{max} model. The C_{ss50} of V_{max}, dp/dt_{max}, and HR inhibitory effects of (+)-Met were larger than those of (−)-Met. **CONCLUSION**: Stereoselective drug distribution and different potencies of the inhibitory effects of (+)-Met and (−)-Met existed in SHR.

Metoprolol (Met) is a β_1-adrenoceptor antagonist used in the treatment of hypertension and coronary disease[1-3]. Like most β-blockers, Met is racemic with 2 stereoisomers: *R*-metoprolol

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[(+)-Met] and S-metoprolol [(−)-Met]. *In vitro*, the β_1-adrenoceptor affinity of (−)-Met in guinea pig left ventricular wall was about 500 times greater than that of (+)-Met[4]. The inhibitory effect of (−)-Met on rabbit heart was 33 times more potent than that of (+)-Met[5]. (−)-Met was more effective than (+)-Met and (±)-Met in reducing mean arterial blood pressure in conscious goat[6]. Our department has demonstrated counterclock-wise hysteresis loops between the inhibitory effects on V_{max}, dp/dt_{max}, LVSP, SBP, heart rate (HR), and (±)-Met blood concentration in normotensive rats and spontaneously hypertensive rats (SHR)[7]. By using Sheiner's effect compartment theory[8], several investigators successfully collapsed some drug hysteresis loops of effect-drug concentration[9,10]. The present study was to establish the combined pharmacokinetic (PK) and pharmacodynamic (PD) model of (+)-Met and (−)-Met, and compare the inhibitory effects between (+)-Met and (−)-Met on negative inotropic effect and negative chronotropic effect in SHR.

MATERIALS AND METHODS

Reagents (+)-Met and (−)-Met tartrates were purchased from Ciba-Geigy Co (Switzerland).

Rats SHR (♀, $n = 15$, weighing 223 ± s 31 g, aged 16 − 20 wk) were purchased from Shanghai Institute of Hypertension Research.

Measurement of myocardial function After the rats were anesthetized with urethan 1 g·kg^{-1} ip, a cannula was advanced into the left ventricular through the right common carotid artery, and then connected to a pressure transducer which was connected to an amplifier and polygraph (RM6000, Nihon Kohen). The right femoral artery was cannulated for measuring the blood pressure (BP) wave similarly. ECG (lead Ⅱ) was observed simultaneously. These 3 signals were input into Pharmacology and Physiology Computer System (PPS, developed by our department), which recorded and calculated 14 indices of cardiovascular function. After ig (+)-Met ($n = 7$) or (−)-Met ($n = 8$) 5 mg·kg^{-1} to SHR, the LVP, BP, and ECG signals were recorded. V_{max}, dp/dt_{max}, LVSP, SBP, and HR were calculated. Blood samples were taken from left femoral artery at 5, 10, 20, 30, 40, 60, 90, and 120 min.

Sample preparation Plasma 100 μL was added to 10 μL of NaOH 2 mol·L^{-1} and 400 μL of ethylacetate. The mixture was vortexed for 10 s and spun at 1000 · g for 10 min. The organic phase was transferred to a tube and evaporated to dryness under N_2 stream. The residue was reconstituted in 100 μL of mobile phase, and 10 μL of this solution was analyzed by HPLC.

Chromatography The HPLC system consisted of a solvent pump (Shimadzu LC-4A, Japan), a 150 mm · 4 mm Shimpack ODS column (Waters Associates, USA), which was heated to 30 ℃. Met concentrations were determined using a fluorescence detector (Shimadzu RF-530, Japan) at λ_{ex} 284 nm and λ_{em} 302 nm. The mobile phase was tetrahydrofuran-water (20∶80) pH 3.0, at 1 mL·min^{-1}. The limit of detection was 5 μg·L^{-1}; the coefficients of variation in both intra- and inter-days were under 3 %; and the recovery was 95 ± s 4 %.

PK-PD model Effect compartment, a PK compartment originally proposed by Sheiner to aid in the correlation of PK and PD of drugs, assume that the hysteresis loop is due to the drug equilibrium course between central compartment and drug effect site. The effect compartment is a hypothetical compartment linked to the central compartment via a first-order rate constant (Fig 1).

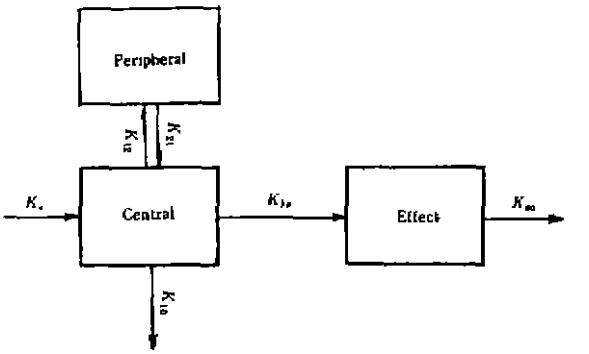

Fig 1. Effect-compartment model in association with a traditional two-compartment open model after ig input.

This compartment receives a negligible amount of actual drug. Hence, the exponential term for the effect compartment does not enter the overall solution for the amount of drug in the body.

For two-compartment model with an ig input, the drug concentration in plasma can be expressed by

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-K_a t} \quad (1)$$

where K_a was absorption rate constant, α was distribution rate constant, and β was elimination rate constant. For the effect compartment model, the equation is

$$dD_e/dt = K_{1e}D_1 - K_{e0}D_e \quad (2)$$

where D_1 and D_e are drug amounts in central compartment and effect compartment, respectively. And K_{1e} is equilibrium rate constant from central compartment to effect compartment, K_{e0} is elimination constant from effect

compartment. When drug in 2 compartments gets equilibium, then $K_{1e}D_1 = K_{e1}D_e$, therefore,

$$K_{e1} = K_{1e}D_1/D_e \quad (3)$$

Utilizing these 3 equations, we get drug concentration in effect compartment:

$$C_e(t) = A'e^{-\alpha t} + B'e^{-\beta t} + C'e^{-K_{e0}t} - (A' + B' + C')e^{-K_{e0}t} \quad (4)$$

where K_{e0} is estimated by simultaneously fitting the PK and PD data using nonlinear regression.

From Eq3, when $K_{e0} < K_{e1}$, K_{e0} expresses not only drug elimination rate from effect compartment, but also drug equilibrium rate between central compartment and effect compartment. Thus, K_{e0} expresses the strength of drug hysteresis. The smaller the value of K_{e0} is, the greater the drug hysteresis loop is.

Statistical analysis The PD parameters were calculated by PPS system. The PK parameters and the PK-PD model parameters were calculated by Computer Aids Pharmacokinetic and Pharmacodynamic (CAPP) Modeling[7]. All data were expressed as $\bar{x} \pm s$. Statistical differences between (+)-Met and (−)-Met groups were determined using t-test.

RESULTS

PK The plasma concentration-time profiles of (+)-Met and (−)-Met were most adequately described by two-compartment model. The V_d values of (+)-Met and (−)-Met were 9.2 ± 1.7 and 7.2 ± 1.7 L·kg^{-1}, respectively ($P < 0.05$). There were no significant differences of other parameters between (+)-Met and (−)-Met (Tab 1, Fig 2).

Tab 1. Pharmacokinetic parameters after ig (+)-Met ($n = 7$) and (−)-Met ($n = 8$) 5 mg·kg^{-1} in SHR. $\bar{x} \pm s$. $^bP < 0.05$ *vs* (+)-Met.

Parameters	(+)-Met	(−)-Met
K_a/min^{-1}	0.18 ± 0.03	0.175 ± 0.027
K_1/min^{-1}	0.021 ± 0.003	0.022 ± 0.003
$T_{\frac{1}{2}K_a}$/min	3.6 ± 1.0	3.6 ± 0.9
$T_{\frac{1}{2}\alpha}$/min	9.6 ± 1.4	8 ± 5
$T_{\frac{1}{2}\beta}$/min	42 ± 8	41 ± 6
C_{max}/mg·L^{-1}	0.49 ± 0.15	0.63 ± 0.13
T_{max}/min	11.5 ± 2.1	11.8 ± 1.7
V_d/L·kg^{-1}	9.2 ± 1.7	7.2 ± 1.7^b
CL/L·min^{-1}·kg^{-1}	0.12 ± 0.03	0.14 ± 0.04
AUC/mg·L^{-1}·min	34 ± 15	42 ± 9

PD After ig (+)-Met or (−)-Met, the peak times of plasma concentration of (+)-Met and (−)-Met were 11.5 ± 2.1 and 11.8 ± 1.7 min, respectively, while the peak effects of V_{max}, dp/dt_{max}, LVSP, SBP, and HR appeared at about 30 − 40 min. There were delays between drug concentration in plasma and their PD responses, resulting in hysteresis in the effect-concentration data. When using the effect compartment model, we estimated the values of K_{e0} on V_{max}, dp/dt_{max}, LVSP, SBP, and HR in rats with CAPP software, and the counterclock-wise hysteresis disappeared. The PK and PD data were fitted by using the sigmoid-E_{max} model after C_e had been calculated:

$$E = E_{max}\, C_e^{\gamma}/(C_e^{\gamma} + C_{ss50}^{\gamma}) \quad (5)$$

where E_{max} was the maximal effect, C_e was the concentration of drug in the effect compartment, C_{ss50} was the concentration of drug in the effect compartment required to achieve 50 % of the maximal response, and γ was power function which effects the sigmoidicity of the relationship[11]. The relationships between predicted and measured effects versus time were illustrated and excellent fits of predicted effects with measured effects were found (Fig 3).

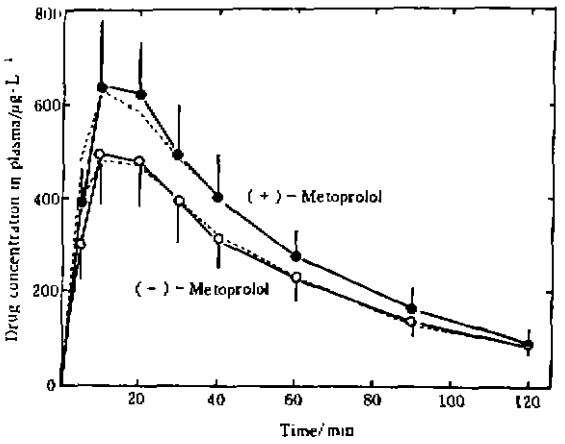

Fig 2. Drug concentrations in plasma after ig (+)-Met and (−)-Met 5 mg·kg^{-1} in SHR. (┈) Predicted.

Significant differences of C_{ss50} on V_{max}, dp/dt_{max}, HR between (+)-Met and (−)-Met were found ($P < 0.01$). C_{ss50+}/C_{ss50-} of V_{max}, dp/dt_{max}, and HR were 11.4, 5.8, and 5.7, respectively. The γ on HR in (+)-Met group was smaller than that in (−)-Met group ($P < 0.05$). There were PD effects on LVSP and SBP in (−)-Met group, but no significant effects on LVSP

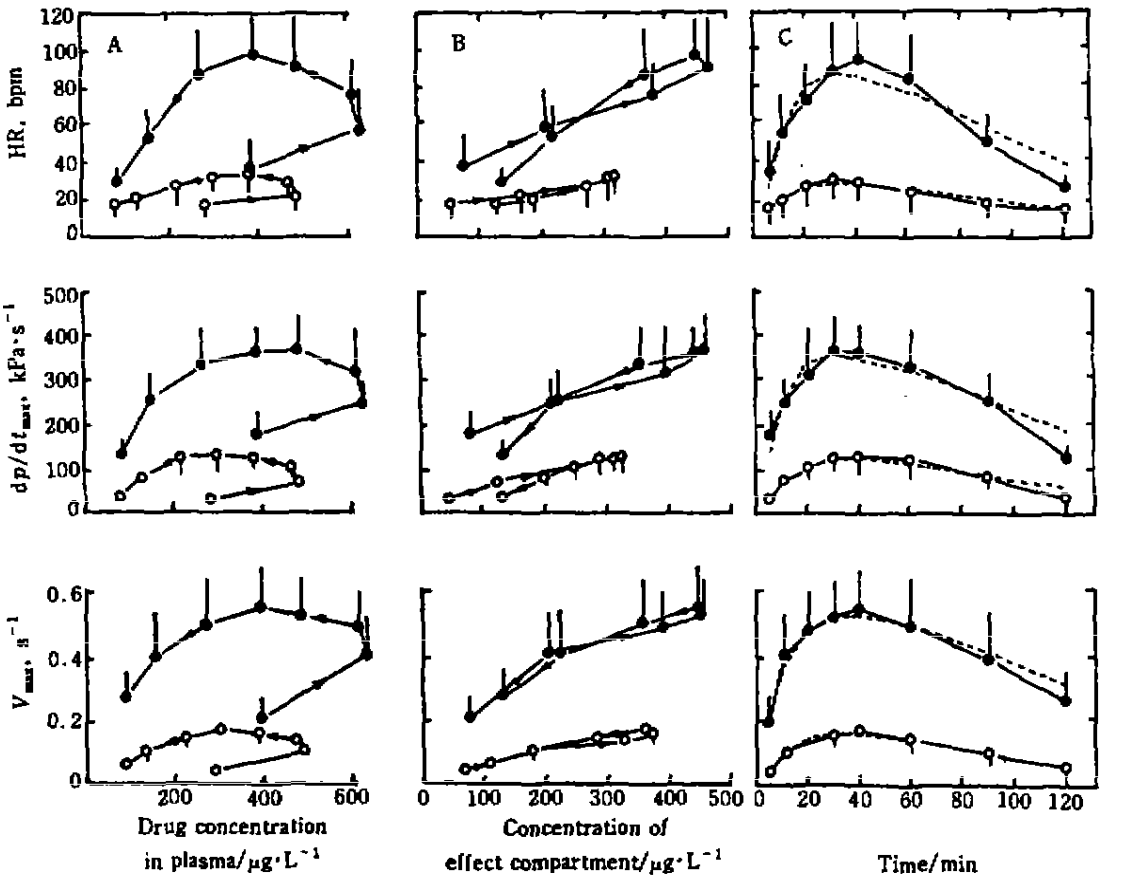

Fig 3. Relationships between inhibitory effects on V_{max}, dp/dt_{max}, HR, and (A) drug concentration in plasma, (B) concentrations of effect compartment, (C) time after ig (+)-Met and (−)-Met 5 mg·kg^{-1} in SHR. (○) (+)-Met observed, (●) (−)-Met observed, (····) predicted.

and SBP in (+)-Met group (Tab 2).

DISCUSSION

The delays between drug concentration in plasma and PD responses indicate that effect compartment is needed in the PK-PD model. When using the CAPP software, we successfully collapsed the hysteresis loops, verifying that our software is well used in the PK-PD model.

The PK parameters show that both (+)-Met and (−)-Met have a rapid absorption phase just like that of (±)-Met[7]. The fact that V_d of (+)-Met was significantly greater than that of (−)-Met indicates the stereo-selectivity in drug distribution, which is due to stereo-selectivity in plasma protein or tissue binding or both[12].

Tab 2. Pharmacodynamic parameters after ig (+)-Met (n = 7) and (−)-Met (n = 8) 5 mg·kg^{-1} in SHR. $\bar{x} \pm s$. $^bP<0.05$. $^cP<0.01$ *vs* (+)-Met.

	E_{max}		C_{ss50}/mg·L^{-1}		γ		K_e/min^{-1}	
	(+)-Met	(−)-Met	(+)-Met	(−)-Met	(+)-Met	(−)-Met	(+)-Met	(−)-Met
V_{max}, s^{-1}	0.8±0.3	0.78±0.28	1.6±0.5	0.14±0.06^c	0.85±0.26	1.1±0.6	0.054±0.023	0.053±0.020
dp/dt_{max}, kPa·s^{-1}	550±40	550±140	1.4±0.4	0.24±0.08^c	1.0±0.6	1.2±0.5	0.054±0.025	0.056±0.018
LVSP, kPa	–	8.0±2.7	–	0.33±0.08	–	2.0±1.6	–	0.047±0.017
SBP, kPa	–	9±3	–	0.30±0.06	–	1.8±1.0	–	0.046±0.021
HR, bpm	110±50	150±60	1.6±0.7	0.28±0.15^c	0.7±0.5	1.5±0.5^b	0.062±0.027	0.060±0.029

C_{ss50+} of inhibitory effects on V_{max}, dp/dt_{max}, and HR were much greater than C_{ss50-}, suggesting that (−)-Met be more potent than (+)-Met in attenuating the inotropic and chronotropic response. The effects of (+)-Met on LVSP and SBP were difficult to be observed in our experiment as compared with those of (−)-Met, suggesting that the affinity for (+)-Met and (−)-Met on β_1-adrenoceptors be different [4].

In sigmoid-E_{max} model, γ demonstrates the receptor combined model. If several drug molecules combine with one receptor: $n(D) + (R) = (D_nR)$, then the number n is the parameter γ in sigmoid-E_{max} model. The difference of γ indicates that the number of (−)-Met molecules combined with one β_1-adrenoceptor is greater than that of (+)-Met.

In conclusion, stereo-selective drug distribution and different potencies of the inhibitory effects on myocardial function of (+)-Met and (−)-Met existed in SHR.

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美托洛尔对映体在自发性高血压大鼠的药动学-药效学结合模型[1]

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关键词 美托洛尔；对映体；药物动力学；药效学；自发性高血压大鼠

目的：研究美托洛尔对映体(+)-Met 和(−)-Met 在麻醉自发性高血压大鼠的药物动力学-药效学结合模型，比较两种对映体对其心血管系统的作用. **方法**：反相高效液相法测定血药浓度，生理记录仪观察药效，计算药动学及药动学-药效学结合模型参数. **结果**：血药浓度-时间曲线符合二室模型. V_d 在两种 Met 之间有显著性差异. 药效和效应室浓度间的关系符合 sigmoid-E_{max} 模型. (+)-Met 抑制 V_{max}，dp/dt_{max} 和 HR 的 C_{ss50} 皆明显大于(−)-Met. **结论**：(+)-Met 和(−)-Met 在 SHR 存在着立体选择性分布，(−)-Met对其心血管系统的抑制作用强于(+)-Met.