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赖诺普利和卡托普利对大鼠心脏钙的影响

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摘要 本文报道了血管紧张素转换酶抑制剂对大鼠心肌的影响. 赖诺普利(Lis) 0.1 μmol·L^{-1}和卡托普利(Cap) 200 μmol·L^{-1}减少缺血再灌大鼠心肌钙的浓度，降低培养新生大鼠心肌细胞内$^{45}Ca^{2+}$的含量，提高心肌 Na^+,K^+—ATPase 的活性. 结果提示减少钙的浓度可能是 Lis 和 Cap 抗大鼠心肌缺血再灌损伤的重要因素之一.

关键词 血管紧张素转换酶抑制剂；培养细胞；心室纤颤；钙放射性同位素；心脏；心肌再灌注损伤

钙

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Plasma bevantolol concentration and heart rate in rabbits

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ABSTRACT Bevantolol (Bev, 5, 10 mg·kg^{-1}) was injected iv to rabbits. A measure the lag time of heart rate (HR) response behind the changes in plasma Bev concentrantion (K_{eo}), and the sensitivity of the site of action of Bev (EC_{50}) were determined. The K_{eo} were 0.03±0.02 and 0.029±0.009 min^{-1} and the EC_{50} were 0.2±0.1 and 0.27±0.14 μg·ml^{-1} respectively for the 2 dosages. The peak changes in HR lagged behind the changes in plasma Bev concentration. There were no significant changes in both pharmacokinetic and pharmacodynamic parameters between the 2 dosages.

KEY WORDS bevantolol; pharmacokinetics; heart rate

Bevantolol (Bev), a cardioselective adrenergic beta receptor blockader has no intrinsic sympathomimetic activity and has weak membrane stabilizing and local anesthetic properties[1]. Bev is effective in the treatment of angina[2] and hypertension[3] in humans and shows anti-arrhythmic and anti-ischemic

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effects in anesthetized pigs subjected to acute left descending coronary artery ligation[4]. The present study was undertaken to correlate the plasma Bev concentration with the heart rate (HR) in rabbits.

MATERIALS AND METHODS

Pure Bev was synthesized by Dr LU Tao (Department of Pharmaceutical Chemistry, China Pharmaceutical University).

Eight rabbits weighing 2.2 ± *s* 0.3 kg (either sex) were equally divided into 2 groups and given an iv dose of Bev 5 or 10 mg · kg^{-1}. The femoral vein was cannulated under local procaine aneasthesia. HR was recorded. Blood samples were taken just before and at 2, 5, 10, 15, 30, 45, 60, 90, 120, 180 min after iv Bev.

Plasma (0.5 ml) was made alkaline with NaOH 1 mol · L^{-1}, and extracted twice with chloroform 3 ml each time (recovery rate of Bev was 97.5%). The residue was dissolved in 60 μl methanol, and 20 μl of the solution was taken for chromatography.

Shimadzu LC—6A high performance liquid chromatograph, Shimadzu SPD—6AV ultraviolet detector, C—R3A HPLC monitor. Zorbax ODS column 25× 0.46 cm ID, mobile phase methanol: 0.01 mol phosphate buffer (pH 7.5) 72 : 28 (vol : vol), flow rate 0.7 ml · min^{-1}. The uv wave-length was 254 nm.

The plasma Bev concentrations were fitted by a nonlinear least-square regression program PKBP-N1[5]. The nonlinear regression program PKPD-CPU[6] was used to calculate the HR.

RESULTS AND DISCUSSION

The plasma Bev concentration-time data were best decribed by a bioexponential equation. The initial distribation of Bev was quick and the terminal elimination phase began at about 40 min, with $T_{\frac{1}{2}\beta}$ of 53.7 ± 9.5 and 45.8 ± 11.5 min, respectively for 5 and 10 mg · kg^{-1}. The volumes of the central compartment were 1.5 ± 0.3 and 2.0 ± 0.5 L · kg^{-1} for the 2 dosages, respectively. The volume of distribution was relatively large, representing the extensive distribution of Bev. There were no significant changes in α, β, V_c, and K_{10} between 5 and 10 mg · kg^{-1} (Tab 1).

Fig 1 shows a 3-dimensional graph to visualize the relationship between the plasma Bev concentration-time-HR, which indicates a significant lag of HR behind the plasma Bev concentration.

Tab 1. Pharmacokinetic and heart rate parameters after iv Bev in rabbits. $n=4$, $\bar{x}\pm s$. $^*P>0.05$ *vs* **5 mg·kg^{-1}.**

Parameters	5 mg·kg^{-1}	10 mg·kg^{-1}
α, min^{-1}	0.17±0.07	0.16±0.06*
β, min^{-1}	0.016±0.003	0.013±0.003*
K_{12}, min^{-1}	0.06±0.02	0.05±0.03*
K_{21}, min^{-1}	0.09±0.05	0.10±0.03*
K_{10}, min^{-1}	0.03±0.01	0.02±0.01*
V_c, L·kg^{-1}	2.0±0.5	1.5±0.3*
S	1.1±0.3	1.0±0.2*
K_{eo}, min^{-1}	0.033±0.018	0.029±0.009*
EC_{50}, μg·ml^{-1}	0.19±0.12	0.27±0.14*
E_{max}, beats·min^{-1}	106±11	121±21*

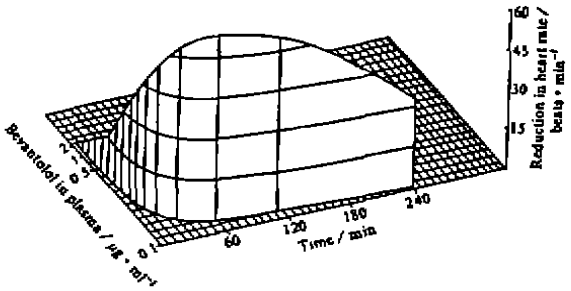

Fig 1. Three-dimensional graph illustrating the plasma drug concentration-time-effect profile after iv bevantolol 5 mg·kg^{-1} in a rabbit.

The resulting data were fitted to the following Hill equation[7]: $E = E_0 - (E_{max} C_e^S)/(EC_{50}^S + C_e^S)$. Here E_0 represents the HR at zero Bev concentration, s is a constant determining the sigmoid shape of the concentration-effect curve, C_e is the Bev concentration in the

hypothetic effect compartment, EC_{50} is the steady-state plasma concentration when the observed effect was 50% of the maximum. The pharmacodynamic parameters estimated by this equation are also shown in Tab 1. The lag times of effect behind the changes in plasma drug concentration $T_{\frac{1}{2}K_{eo}}$, were 27.3 ± 16.7 and 25.9 ± 7.3 min respectively for the 2 dosages, showing a significant lag of its effect on HR behind plasma Bev concentratoin. The assumption that the observed effect was related to the central (plasma) compartment appeared to be valid, as shown by the relationships of the pharmacokinetic rate constants α and β and the pharmacodynamic rate ocnstant K_{eo}. When $K_{eo} < \beta$, the amount in the effect compartment would persist longer than the drug concentration in plasma, and if $\alpha > K_{eo} > \beta$, the terminal elimination of the amount in the effect compartment would be parallel with that of the drug in plasma[5]. EC_{50} were 0.2 ± 0.1 and 0.27 ± 0.14 $\mu g \cdot ml^{-1}$ respectively for the 2 dosages, representing the high sensitivity of the site of action of Bev. There seemed to be some differences ($P > 0.05$) for both EC_{50} and E_{max} following iv Bev.

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贝凡洛尔在兔的血药浓度与心率的关系

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摘要 用药物动力学—药效学结合模型(PK-PD)，对兔贝凡洛尔血药浓度与心率的关系作定量分析，兔iv贝凡洛尔后，其心率变化明显滞后于血药浓度的变化，用PK-PD模型估算了其效应动力学参数 K_{eo} 和 EC_{50}：兔iv 5，10 $mg \cdot kg^{-1}$ 后，K_{eo} 分别为0.03 ± 0.02，0.029 ± 0.009 min^{-1}，EC_{50} 分别为0.2 ± 0.1，0.27 ± 0.14 $\mu g \cdot ml^{-1}$。

关键词 贝凡洛尔；药物动力学；心率

药代动力学 血液

新 书 预 告

由我国抗炎、免疫药理学的奠基人周金黄教授倡议并主编的《免疫药理学进展：基础与临床》，将于1993年5月正式出版。本书汇集了我国从事免疫药物研究的专家撰写的以本人研究专题为主的论文或综述30余篇，反映了我国抗炎、免疫的药理科研工作十年来的进展，可供广大医药科研和教学工作者参考，全书共41万字，三十二开本584页，每册定价15.50元。欲定购者请速与 100850 北京市太平路27号军事医学科学院《院报》编辑室王国展主任联系。