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Pharmacokinetics of *m*-nifedipine in rabbits after intravenous injection

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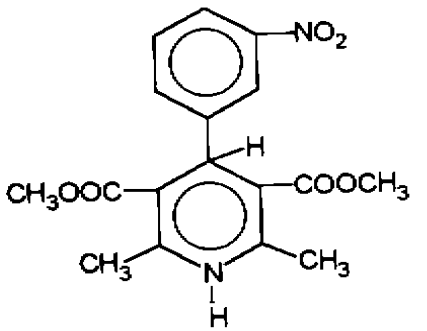
KEY WORDS *m*-nifedipine; high pressure liquid chromatography; pharmacokinetics; dihydropyridines

AIM: To study the dose effects on pharmacokinetics of *m*-Nif. **METHODS**: Fifteen rabbits were divided into 3 groups receiving iv *m*-Nif 0.5, 1, and 2 $mg \cdot kg^{-1}$. Plasma levels of *m*-Nif were determined with HPLC method. **RESULTS**: The concentration-time data were fitted with 2-compartment model. After iv 1 $mg \cdot kg^{-1}$, the parameters were: $V_d = 0.37 \pm 0.10\ L \cdot kg^{-1}$, $T_{\frac{1}{2}\alpha} = 6.4 \pm 2.9$ min, $T_{\frac{1}{2}\beta} = 84 \pm 22$ min, $AUC = 94 \pm 16\ mg \cdot min \cdot L^{-1}$, $Cl = 0.65 \pm 0.13\ L \cdot kg^{-1} \cdot h^{-1}$. No statistically significant difference was found in Cl and $T_{\frac{1}{2}\beta}$ between 3 dose groups. AUC (standardized to body weight) was correlated with doses. **CONCLUSIONS**: *m*-Nif was distributed widely and eliminated at a fairly rapid rate in the rabbits. No dose-dependent pharmacokinetics was found after iv *m*-Nif 0.5 - 2 $mg \cdot kg^{-1}$.

m-Nifedipine, 2, 6-dimethyl-3, 5-dicarbomethoxy-4-(3′-nitrophenyl)-1, 4-dihydropyridine (*m*-Nif) is a new calcium channel blocker. Dihydropyridine calcium channel antagonists are mainly used for the treatment of hypertension and angina[1]. Nifedipine is susceptible to photodegradation, but *m*-Nif is stable when exposed to light. The 2 drugs have the same antihypertensive effect[2]. So far, no report has been found on pharmacokinetics of *m*-Nif.



m-Nifedipine

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Using a high performance liquid chromatographic (HPLC) method, we studied the dose effects on the pharmacokinetics of iv *m*-Nif 0.5, 1, and 2 $mg \cdot kg^{-1}$ in conscious rabbits.

MATERIALS AND METHODS

Drug and reagents *m*-Nif and internal standard (2, 6-dimethyl-3, 5-dicarbomethoxy-4-phenyl-1, 4-dihydropyridine) were synthesized by Prof MEI Qi-Bin (Department of Pharmacology, Fourth Military Medical University), purity >98 %. All other chemical reagents were of AR. An injection of *m*-Nif was prepared at 2 $g \cdot L^{-1}$ in 70 % polyethylene glycol (PEG) and stored in the dark.

Instruments The LC-6A HPLC system (Shimadzu Corp, Kyoto, Japan) consisted of an SPD-6AV uv-vis spectrophotometric detector and a C-R3A data processing unit. A 100 mm × 46 mm rapid analytical columm (Dalian Institute of Chemical Physics) were packed with Spherisorb C_{18} 3 μm.

Rabbits Newzealand white rabbits (♂, $n = 15$), weighing 2.4 ± 0.2 kg were provided by Animal Center of Fourth Military Medical University.

Protocol Fifteen rabbits were randomizedly divided into 3 groups ($n = 5$ each) and received iv *m*-Nif 0.5, 1, and 2 $mg \cdot kg^{-1}$, respectively. The injection was over a period of 2 min. Blood samples were collected from another ear at 4, 10, 25, 60, 120, 240, and 360 min after iv *m*-Nif.

Plasma sampling The plasma (0.50 mL) was added 24 μL of internal standard (10 $mg \cdot L^{-1}$) and extracted with 3.00 mL diethyl ether by swirl shaking at 18 ℃ for 4 min. After being centrifuged at 800 × *g* for 5 min, 2.00 mL of the ether phase was evaporated at 40 ℃ under a gentle air flow. The residue was dissolved with 80 μL of methanol, and 20 μL of the solution were injected for HPLC analysis.

Assay The plasma *m*-Nif concentration was analyzed with an HPLC system[3,4,6]. Methanol-water (45:20, vol: vol) was used as mobile phase at a flow rate of 0.65 mL $\cdot min^{-1}$. The detector was set at 350 nm and 0.02 AUFS. The retenion time of *m*-Nif was 7.0 min. The plasma detection limit was 10 $\mu g \cdot L^{-1}$. The linear range was between

0 – 5760 mg·L^{-1} with recoveries of 90 % ± 3 % at different levels and CV < 7 % (within-day) and < 10 % (between-days).

Pharmacokinetic analysis The concentrations were analyzed with a 3P87 of the Chinese Pharmacological Society on a COMPAQ-386 personal computer to determine the compartment models and the pharmacokinetic parameters. Comparisons of 3 doses were carried out with F-test. Correlation between dose and AUC was determined by least-squares linear regression.

RESULTS

The plasma m-Nif concentrations after iv 0.5, 1, and 2 mg·kg^{-1} were best fitted with 2-compartment model (Tab 1).

Tab 1. m-Nif levels in plasma (mg·L^{-1}) after iv 3 doses in rabbits. $n = 5$, $\bar{x} \pm s$.

Time/min	0.5 mg·kg^{-1}	1 mg·kg^{-1}	2 mg·kg^{-1}
4	1 012 ± 12	1 790 ± 152	3 963 ± 318
10	840 ± 88	1 206 ± 217	2 277 ± 440
25	336 ± 63	662 ± 71	1 307 ± 109
60	253 ± 50	393 ± 54	826 ± 38
120	160 ± 62	234 ± 82	421 ± 56
240	63 ± 13	80 ± 19	186 ± 64
360	32 ± 16	48 ± 18	121 ± 14

No statistically significant difference was found in $T_{\frac{1}{2}\beta}$, Cl between the 3 dose groups when analyzed with F-test (Tab 2).

Tab 2. Pharmacokinetic parameters of m-Nif after iv 3 doses in rabbits. $n = 5$, $\bar{x} \pm s$. $^{a}P > 0.05$ (comparisons of 3 dose groups with F-test).

	0.5 mg·kg^{-1}	1 mg·kg^{-1}	2 mg·kg^{-1}
A/mg·L^{-1}	1.3 ± 0.8	2.3 ± 1.0	4.8 ± 1.6
B/mg·L^{-1}	0.3 ± 0.2	0.58 ± 0.09	1.1 ± 0.7
V_d/L·kg^{-1}	0.35 ± 0.01	0.37 ± 0.10	0.32 ± 0.05
$T_{\frac{1}{2}\alpha}$/min	7.8 ± 0.5	6.4 ± 2.9	5.0 ± 2.3
$T_{\frac{1}{2}\beta}$/min	88 ± 5^{a}	84 ± 22^{a}	90 ± 23^{a}
K_{10}/min^{-1}	0.03 ± 0.01	0.03 ± 0.02	0.03 ± 0.01
K_{21}/min^{-1}	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01
K_{12}/min^{-1}	0.06 ± 0.01	0.06 ± 0.02	0.07 ± 0.02
AUC/mg·min·L^{-1}	54 ± 14	94 ± 16	198 ± 28
Cl/L·kg^{-1}·h^{-1}	0.58 ± 0.12^{a}	0.65 ± 0.13^{a}	0.61 ± 0.08^{a}

The relationship between dose and AUC, standardized by body weight, showed a significant correlation ($r = 0.9524$, $P < 0.01$).

DISCUSSION

m-Nif after iv conformed to 2-compartment model, with pharmacokinetic parameters of V_d 0.37 L·kg^{-1}, demonstrating that m-Nif was distributed widely in the rabbits. The drug was eliminated rapidly from the plasma compartment with $T_{\frac{1}{2}\beta}$ 84.1 min and Cl 0.65 L·kg^{-1}·h^{-1}. These parameters are similar to data of nifedipine ($T_{\frac{1}{2}\beta}$ 1.77 h, Cl 0.62 L·kg^{-1}·h^{-1}), suggesting that 2 isomers of m-Nif and nifedipine have the same process of pharmacokinetics[5].

No statistically significant difference existed in Cl, $T_{\frac{1}{2}\beta}$ when analyzed for equivalence across the 3 doses. AUC showed a linear relationship with dosages. In summary, no dose-dependent pharmacokinetics was found after iv m-Nif 0.5 – 2 mg·kg^{-1}.

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间硝苯地平在兔体内的药物动力学

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关键词 间硝苯地平；高压液相色谱法；药物动

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力学；二氢吡啶类

目的：研究间硝苯地平剂量效应的药代动力学. **方法**：兔被随机分成三组，分别静脉注射高、中、低(0.5, 1, 2 mg·kg^{-1})三种剂量的间硝苯地平，用 HPLC 法测定血浆药物浓度. **结果**：间硝苯地平的血药浓度和时间数据经拟合均符合二室模型，主要药动学参数如下(以剂量 1 mg·kg^{-1}为例)：V_d = 0.37 L·kg^{-1}，$T_{\frac{1}{2}\alpha}$ = 6.4 min，$T_{\frac{1}{2}\beta}$ = 84.1 min，AUC = 94.1 mg·min·L^{-1}，Cl = 0.65 L·kg^{-1}·h^{-1}. 各剂量组间的 Cl，$T_{\frac{1}{2}\beta}$经方差分析无显著差异，用单位体重的曲线下面积对剂量进行线性回归存在显著正相关. **结论**：间硝苯地平分布广，消除也迅速；在剂量 0.5－2 mg·kg^{-1}范围内消除动力学呈非剂量依赖性关系.

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Mapping of preproenkephalin mRNA in brain of spontaneously hypertensive rats[1]

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KEY WORDS hypertension; preproenkephalin; messenger RNA; *in situ* hybridization; brain; inbred SHR rats; inbred WKY rats

AIM: To detect different expression of preproenkephalin mRNA (PPE mRNA) in 16-wk-old spontaneously hypertensive rat (SHR) and age-matched normotensive Wistar-Kyoto rat (WKY). **METHODS**: Nonradioactive *in situ* hybridization was performed using digoxigenin-labeled RNA probe. **RESULTS**: Compared with WKY rats, PPE mRNA levels of 16-wk-old SHR increased in hypothalamic nuclei (>20), amygdaloid nuclei (>23), ventrolateral central gray (21.2), reticular substantia nigra (21.5), interpeduncular nuclei (>21), nucleus of the solitary tract (30.7), rostroventrolateral reticular nucleus (29.1), gigantocellular reticular nucleus (23.9) and thoracic spinal cord (>30); decreased in dorsal central gray (22.7). No difference was found in compact substantia nigra (22.8), dentate gyrus (26.2) and CA1, CA2, CA3 of hippocampus (>25). **CONCLUSION**: PPE mRNA in brain regions involved in modulation of blood pressure may be associated with the genesis of spontaneous hypertension in SHR.

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Enkephalin, an endogenous ligand of opioid receptors, is important in the regulation of blood pressure (BP). Intracerebroventricular injection (icv) of μ agonist [D-Ala^2-MePhe^4-Gly^5-ol]-enkephalin (DAGO) and δ agonist [D-Ala^2, D-Leu^5]-enkephalin (DADLE) increased the BP[1]. *In situ* hybridization study showed preproenkephalin mRNA was localized in hypothalamic nuclei, hippocampus, NTS, and spinal cord[2], where the cardiovascular regulation took place.

The icv of μ agonist morphiceptin induced a pressor response in SHR but hypotension in WKY rat, and δ agonist Tyr-D-Thr-Gly-Phe-Leu-Thr (DTLET) icv decreased BP in SHR but increased BP in WKY[3]. Compared with WKY rats, SHR had greater concentration of methionine-enkephalin (Met-Enk) in cortex, pons, and medulla[4], but lower Leu-Enk in suprachiasmatic nucleus[5]. These studies imply that opiate system is disturbed in essential hypertension.

The aim of this study is to determine whether the biosynthetic activity of CNS opiates in brain is altered in case of essential hypertension.

MATERIALS AND METHODS

SHR and WKY rats (aged 16 wk, ♂, n = 5, weighing 268 ± s 6 g and 310 ± s 12 g, respectively) were purchased from Department of Pharmacology, Second Military Medical