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Antihypertensive effects of *m*-nisoldipine and nisoldipine on conscious renal hypertensive rats and dogs

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ABSTRACT The antihypertensive effects of *m*-nisoldipine (*m*-Nis) and nisoldipine (Nis) by ig 0.3, 1.0, 3.0 and 1.0, 3.0, 9.0 mg · kg^{-1} respectively on renal hypertensive rats (RHR) and 0.1, 0.3, 1.0 mg · kg^{-1} orally (for both drugs) on renal hypertensive dogs (RHD) were studied. Both *m*-Nis and Nis depressed blood pressure (BP) dose-dependently in RHR and RHD. The reduction of blood pressure correlated well with the *m*-Nis concentration in plasma of RHD. On the basis of ED_{20} (HR) / ED_{20} (BP), the hypotensive effect of *m*-Nis on systolic blood pressure (SBP) was only 1.6 times as great as that of Nis on RHR ($P<0.05$), but in RHD, both drugs showed the same potency ($P>0.05$). In both models, *m*-Nis showed much more potent effect on diastolic blood pressure (DBP) than Nis ($P<0.01$), and possessed stronger hypotensive effects on DBP than on SBP ($P<0.05$ and $P<0.01$); but for Nis, its effects on SBP and DBP appeared to be in the same order ($P>0.05$). The fall in BP was accompanied by a transient increase of heart rates (HR) with *m*-Nis and Nis in RHR and RHD. The chronic antihypertensive effects of *m*-Nis and Nis were also remarkable with 1.0 mg · kg^{-1} daily at 9 AM for 21 d. During this period, the BP and HR lowered to nearly normal level. After withdrawal of *m*-Nis and Nis, the hypotensive effects lasted nearly 1 wk.

KEY WORDS antihypertensive agents; renovascular hypertension; dogs; rats; *m*-nisoldipine; nisoldipine

Nisoldipine (Nis) possessed vascular selectivity and exhibited a long-lasting hypotensive effects on renal hypertensive dogs (RHD)[1,2]. *m*-Nis was first developed in the Department of Organic Chemistry, Hebei Medical College, and our previous papers reported that *m*-Nis shared the same characteristics as Nis and was much more stabe to sunlight and heat compared with Nis[3-8].

The present study was undertaken to evaluate the effectiveness of *m*-Nis in RHR and RHD and its plasma concentrations.

MATERIALS AND METHODS

Renal hypertensive rats The ♂ Sprague-Dawley rats, weighing 150 ± *s* 16 g were used to prepare RHR (1K1C) by clipping the renal artery[9]. After operation, rats received a standard diet and saline. After 8 wk, body weight increased to 315 ± 14 g and BP reached 22.7 / 18.0-25.3 / 21.3 kPa were used in the experiments. Groups of 8 RHR were used to test the hypotensive effects of *m*-Nis and Nis (supported by the Department of Pharmacy of our College). *m*-Nis and Nis were protected from light in all the procedures. The drugs were suspended in 0.5% carboxymethylcellulose (CMC) and giving at a volume of 3 ml · kg^{-1} by stomach tube. SBP, DBP, and HR were monitered before and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 h after ig by tail cuff method[9]. RHR were allowed to take saline *ad lib* but no food for 24 h in the laboratory at 30℃ before the experiments.

Renal hypertensive dogs Dogs, both sexes, weighing 15 ± 4 kg were prepared (2K1C) by renal artery constriction[10]. At the same time, a left carotid artery loop was made. After operation, the dogs were injected im penicillin 800 000 u at 9 AM and 5 PM daily, and kept in the laboratory with room temperature of 20℃ for 10 d. RHD with BP above 21.3 / 17.3 kPa were employed

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in the experiments. SBP, DBP, and HR were measured on the carotid artery loop with a stethoscope.

m–Nis and Nis were freshly suspended in 0.5% CMC (0.1 mg · kg^{-1} group) or weighted accurately (0.3 and 1.0 mg · kg^{-1} groups) just before the test. the drugs in the meat soup were given orally according to a cross–over design. The washout period of a drug was 5 d before the subsequent experiment. *m*–Nis and Nis were protected from light also. In the chronic test, the RHD were given *m*–Nis or Nis 1.0 mg · kg^{-1} at 9 AM daily for 21 d.

The plasma concentration of *m*–Nis was measured in RHD with 0.3 and 1.0 mg · kg^{-1} single doses with HPLC[11–13].

Statistical analysis Values were expressed as the $\bar{x} \pm s$. Comparason between values before and after medication was carried out with paired *t* test. Correlation coefficient was caculated by linear regression analysis. The doses required to decrease BP or increase HR by 20% of the initial values (ED_{20}) were meassured[14].

RESULTS

Antihypertensive effects of *m*–Nis and Nis on RHR The reductions of SBP and DBP were seen after 30 min and reached the peak effects at 1 h after medication. The maximal depressive duration of *m*–Nis and Nis were about 8 and 6 h (on SBP), 8 and 12 h (on DBP) respectively. At 1 and 3 mg · kg^{-1} (*m*–Nis) or 3 and 9 mg · kg^{-1} (Nis), transient increases of HR were seen from 30 min to 3 h after dosing (Fig 1).

Antihypertensive effects of *m*–Nis and Nis on RHD The hypotensive effects started from 30 min and the maximal effects attained at 1 h after medication. The maximal hypotensive duration of *m*–Nis or Nis lasted 6 and 6 h (on SBP) or 8 and 6 h (on DBP) respectively with the largest dose. There was

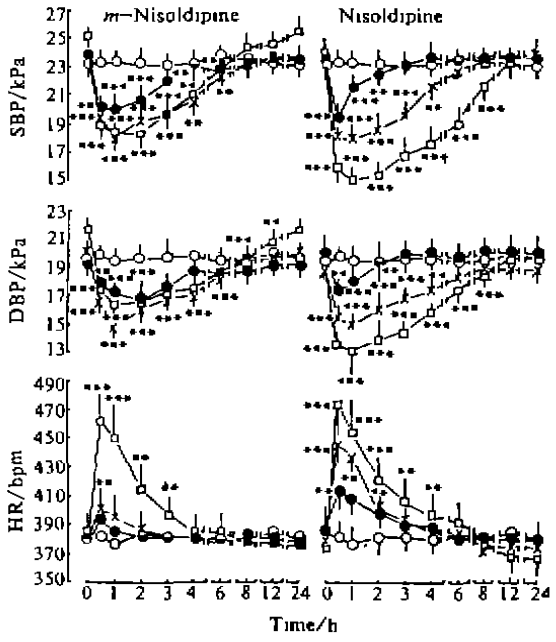

Fig 1. Effects of single ig dose of *m*–nisoldipine or nisoldipine in conscious renal hypertensive rats. $n=8$, ○ control (CMC), ● 0.3, × 1.0, □ 3.0 mg · kg^{-1} for *m*–Nis in 0.5% CMC solution; ● 1.0, × 3.0, □ 9.0 mg · kg^{-1} for Nis in 0.5% CMC. $\bar{x} \pm s$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* before.

also a transient positive chronotropic effect at 1–8 h, but the peak effects occurred at about 3 h after oral dosing (Fig 2).

Plasma concentration of *m*–Nis in RHD The plasma concentrations of *m*–Nis with single doses of 0.3 or 1.0 mg · kg^{-1} correlated well with the reduction of BP ($r=0.9987$) (Fig 3).

Chronic antihypertensive effects of *m*–Nis and Nis on RHD During the 21 d treatment with both drugs, there were no positive chronotropic effects, but the BP were reduced from d 3 and persisted in a lower and stable state. After withdrawal of both drugs, the hypotensive effects lasted nearly 1 wk (Fig 4).

DISCUSSION

In RHR, the ED_{20} value of Nis for

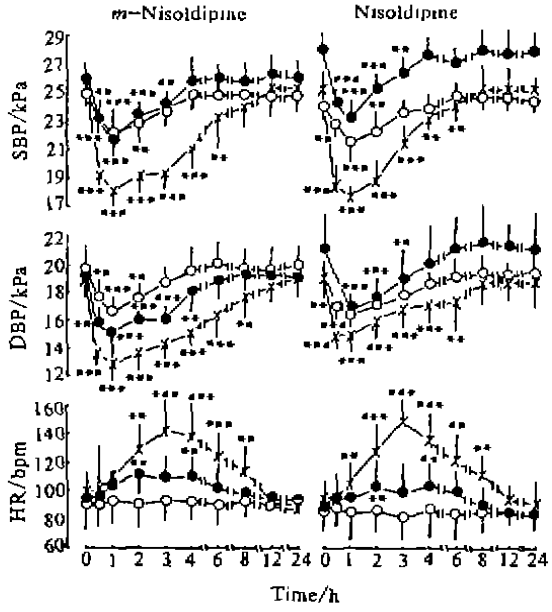

Fig 2. Effects of single oral dose of *m*-Nis or Nis on conscious renal hypertensive dogs. $n=6$, ○ 0.1, ● 0.3, × 1.0 mg · kg^{-1} for both drugs. $\bar{x} \pm s$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* before.

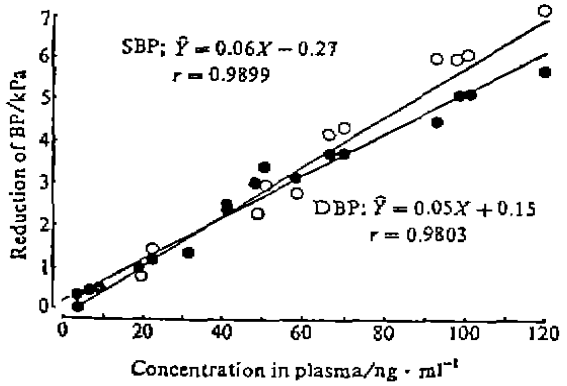

Fig 3. Plasma concentrations of *m*-Nis *vs* reductions of systolic (○) and diastolic (●) blood pressures from 6 renal hypertensive dogs with single oral dose of 0.3 or 1.0 mg · kg^{-1}. $\bar{x} \pm s$.

HR, SBP or DBP was 1 to 5 times greater than that of *m*-Nis, which suggested that *m*-Nis was more potent on these three parameters. But in RHD, the ED_{20} value of

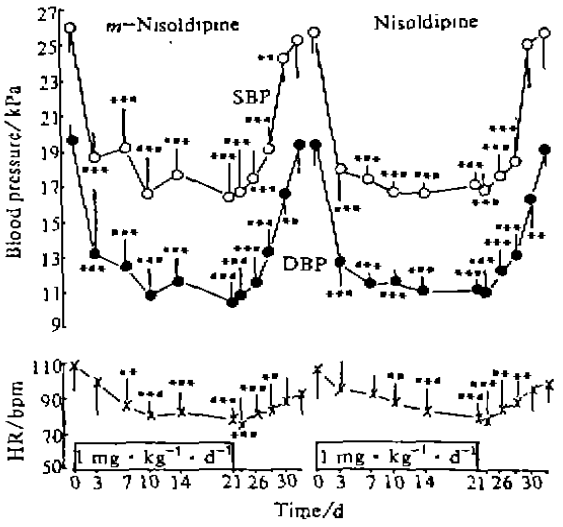

Fig 4. Effects of *m*-Nis and Nis, both 1.0 mg · kg^{-1} · d^{-1} × 21 d on renal hypertensive dogs. $\bar{x} \pm s$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* before.

m-Nis on HR or SBP was almost equal to what of Nis respectively. Only the ED_{20} value of Nis on DBP was 2 times as great as what of *m*-Nis, which disagreed with our previous results in anesthetized normotensive dogs[3]. These differences may be due to the species and the conditions of animals. So according to the ED_{20} values, it is suggested that *m*-Nis could reduce the DBP predominiently compared with Nis in conscious RHD (Tab 1).

On the basis of ED_{20} (HR)/ED_{20} (BP), our results demonstrated that *m*-Nis reduced the SBP a little greater than Nis in RHR, but in RHD, both drugs showed the same potent hypotensive effect on SBP; the potency of *m*-Nis to reduce DBP was 1 time higher than Nis in both models, and the reduction of DBP induced by *m*-Nis was 0.5 to 1 time greater than that of SBP. During the chronic treatment with both drugs, the blood pressure was reduced down to nearly normal levels. And from d 3 to the end of treatment, the blood pressure persisted in a lower and stable state. Along with the

Tab 1. ED_{20} of *m*-nisoldipine or nisoldipine on renal hypertensive dogs (RHD) and rats (RHR). ED_{20} = the dose to reduce BP or increase HR by 20%.

	m-Nis	Nis
ED_{20} / mg · kg^{-1}		
RHR (n=24, ig)		
HR	3.45	7.85
SBP	0.87	3.19
DBP	0.60	3.08
RHD (n=18, po)		
HR	2.13	2.00
SBP	0.54	0.49
DBP	0.27	0.56
ED_{20} (HR)/ ED_{20} (SBP)		
RHR	3.96	2.46
RHD	3.94	4.08
ED_{20} (HR)/ ED_{20} (DBP)		
RHR	5.75	2.55
RHD	7.89	3.57

reduction of blood pressure, there were no increase of HR but a negative chronotropic effects disclosed.

As a result, our experiments demonstrated that *m*-Nis possessed potent antihypertensive effects on RHR and RHD, especially reduced DBP predominently in both hypertensive models compared with Nis.

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间尼索地平和尼索地平对清醒肾性高血压大鼠及犬的抗高血压作用

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提要 间尼索地平(*m*-Nis)降低 SBP 在肾性高血压大鼠(RHR，ig)强于尼索地平(Nis，$P<0.05$)；在肾性高血压犬(RHD，*po*)相近($P>0.05$)，降压作用与其血药浓度呈正相关．在 RHR 和 RHD，*m*-Nis 降低 DBP 强于 Nis ($P<0.01$)，优于降低 SBP ($P<0.05$ 和 $P<0.01$)．Nis 对 SBP 和 DBP 作用相似($P>0.05$)．降压作用均伴有心率加快．连续灌服 21 天，明显而平稳地降低 RHD 血压，停药后仍持续约一周．

关键词 降压剂；肾血管高血压；犬；大鼠；间尼索地平；尼索地平

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钩藤碱和异钩藤碱对麻醉犬血压及器官血流的作用[1]

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Effects of rhynchophylline and isorhynchophylline on blood pressure and blood flow of organs in anesthetized dogs

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ABSTRACT In anesthetized thoracotomized dogs, rhynchophylline (Rhy 5 mg · kg^{-1}, iv) reduced the mean arterial pressure (MAP), heart rate (HR), and coronary blood flow (CBF) by 1.16± *s* 0.67 kPa, 19± 12 beats / min, and 0.12± 0.04 ml · min^{-1} · g^{-1}, whereas isorhynchophylline (Isorhy 1 mg · kg^{-1}, iv) reduced the parameters by 3.58± 0.19 kPa, 26± 18 beats / min, and 0.10± 0.04 ml · min^{-1} · g^{-1}, respectively. In unthoracotomized dogs, Rhy (10 mg · kg^{-1}, iv) decreased renal blood flow (RBF) by 0.35± 0.16 ml · min^{-1} · g^{-1}, but did not change the MAP. Isorhy (5 mg · kg^{-1}, iv) reduced the MAP by 3.44± 1.44 kPa, but the RBF remained unaffected. These results indicated that the hypotensive effect of Isorhy in a dosage not affecting RBF was more potent than that of Rhy.

KEY WORDS rhynchophylline; isorhynchophylline; blood pressure; blood flow velocity; hemodynamics; oxygen consumption

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提要 Rhy 5 mg · kg^{-1} iv 使麻醉开胸犬的 MAP，HR 及 CBF 分别下降 1.16± *s* 0.67 kPa，19± 12 beats / min 及 0.12± 0.04 ml · min^{-1} · g^{-1}，Isorhy 1 mg · kg^{-1} iv 使上述指标分别下降 3.58± 0.19 kPa，26± 18 beats / min 和 0.10± 0.04 ml · min^{-1} · g^{-1}；在未开胸犬，Rhy 10 mg · kg^{-1} iv 对 MAP 无明显影响，但 RBF 减少 0.35± 0.16 ml · min^{-1} · g^{-1}，Isorhy 5 mg · kg^{-1} iv 使 MAP 降低 3.44± 1.44 kPa 而 RBF 不变．结果提示 Isorhy 的降压作用强于 Rhy 且对 RBF 无不良影响．

关键词 钩藤碱；异钩藤碱；血压；血流速度；血液动力学；氧消耗