

## Effects of 3'-angeloyloxy-4'-acetoxy-3', 4'-dihydroseselin on cardiohemodynamics in anesthetized dogs

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**ABSTRACT** Cardiohemodynamic effects of 3'-angeloyloxy-4'-acetoxy-3', 4'-dihydroseselin (Pd-Ia) isolated from the Chinese medicinal plant *Peucedanum praeruptorum* Dunn were compared with those of diltiazem (Dil) in anesthetized open-chest dogs. Pd-Ia 3 mg·kg<sup>-1</sup> increased coronary blood flow from 25±11 to 58±16 ml·min<sup>-1</sup> (n=7, P<0.01) and decreased mean aortic pressure (MAP) from 13±2 to 8±1 kPa (P<0.01), rate pressure product (RPP) from 1.9±0.5 to 1.3±0.3 MPa·bpm (P<0.05), +dp/dt<sub>max</sub> from 246±56 to 160±36 kPa·s<sup>-1</sup> (P<0.01) and systemic vascular resistance from 19±4 to 12±7 Pa·ml<sup>-1</sup>·min<sup>-1</sup> (P<0.05), together with an increase in HR. Dil showed effects similar to those of Pd-Ia except for a marked decrease in HR. The effects of Pd-Ia on MAP and RPP were approximately one-tenth as potent as those of Dil. The results demonstrated that Pd-Ia was a Ca<sup>2+</sup> channel blocker.

**KEY WORDS** 3'-angeloyloxy-4'-acetoxy-3', 4'-dihydroseselin; coumarins; *Peucedanum praeruptorum*; hemodynamics; calcium channel blockers; diltiazem

A Chinese herb "qian-hu" (*Peucedanum*) is commonly used for the treatment of chest pain. Our previous studies showed that the

crude extract of "bai-hua" qian-hu (*Peucedanum praeruptorum* Dunn; Umbelliferae) increased coronary blood flow (CBF) in isolated rabbit hearts and decreased blood pressure in anesthetized cats<sup>(1)</sup>. The racemic 3'-angeloyloxy-4'-acetoxy-3', 4'-dihydroseselin<sup>(2)</sup> (Pd-Ia) isolated from the root was found to inhibit the influx of <sup>45</sup>Ca<sup>2+</sup> into the smooth muscle cells of isolated guinea pig taenia coli<sup>(3)</sup> and relax the isolated dog coronary artery contracted by calcium<sup>(4)</sup>. Using patch clamp technic in single ventricular cell of guinea pig hearts, we found that Pd-Ia reduced the action potential duration and Ca<sup>2+</sup> currents dose-dependently, and it appeared as a Ca<sup>2+</sup> channel blocker<sup>(5)</sup>. The present study was to compare the effects of Pd-Ia on cardiohemodynamics with those of diltiazem (Dil) in anesthetized open-chest dogs.

### MATERIALS AND METHODS

**Drugs** Pd-Ia, a white powder with mp 156-158 °C<sup>(6)</sup>, was extracted at Department of Pharmacognosy and Phytochemistry, Meiji College of Pharmacy, Japan. Pd-Ia and Dil (Sigma, USA) were dissolved in polyethylene glycol (PEG) 200 and 0.9 % saline, respectively. The drug solutions were freshly prepared before experiment.

**Dogs** Thirteen mongrel dogs of both sexes, weighing 8-16 kg after an overnight fast were anesthetized with thiopental sodium 20 mg·kg<sup>-1</sup> iv and ventilated through an endotracheal tube with O<sub>2</sub> and N<sub>2</sub>O (1:2) to which 0.8-1.5 % enflurane was added. The right femoral vein and artery were cannulated for drug injection and aortic pressure recording, respectively. A left thoracotomy was performed at

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the 5th intercostal space and the heart was suspended in a pericardial cradle. A microtip pressure catheter was inserted into the left ventricle through a small incision in the apex. Left ventricular end-diastolic pressure (LVEDP), its first derivative (LV  $dp/dt$ ) and heart rate (HR) were recorded. Two sizes of electromagnetic probes were placed around the aorta and left circumflex for the measurements of cardiac output (CO) and CBF, respectively. Systemic vascular resistance (SVR) and stroke volume (SV) were calculated as the quotients of MAP and mean CO and of mean CO and HR, respectively. Rate pressure product (RPP), an indirect index of myocardial  $O_2$  consumption, was calculated as the product of SAP and HR<sup>(7)</sup>.

**Experimental protocol** The dog was allowed to stabilize for at least 1 h and control hemodynamic parameters were obtained. Seven dogs were injected iv with Pd-Ia (0.1–3 mg·kg<sup>-1</sup>) and its solvent PEG solution, and another 6 dogs with Dil (0.03–1 mg·kg<sup>-1</sup>) and saline. Each dose was injected over 15 s in an increment fashion followed by a flush with saline 2 ml after recovery of hemodynamic changes induced by the previous dose.

**Statistical analysis** The values in each cardiohemodynamic parameter within a group were compared with the baseline value immediately before the iv injection of Pd-Ia or Dil using paired *t* test. Comparison of cardiohemodynamic parameters before and after the injection of Pd-Ia or vehicle was performed using one-way ANOVA.

## RESULTS

Pd-Ia 1–3 mg·kg<sup>-1</sup> dose-dependently caused increases in mean CBF and HR, and decreases in SAP, MAP, SVR, RPP and +LV  $dp/dt_{max}$ . At 3 mg·kg<sup>-1</sup>, it increased mean CBF from 25±11 to 58±16 ml·min<sup>-1</sup> ( $n=7$ ,  $P<0.01$ ) and HR from 100±24 to 139±24 bpm ( $P<0.05$ ), and decreased MAP from 13±2 to 8±1 kPa ( $P<0.01$ ), SVR from 19±4 to 12±7 Pa·ml<sup>-1</sup>·min<sup>-1</sup> ( $P<0.05$ ), RPP from 1.9±0.5 to 1.3±0.3 MPa·bpm ( $P<0.05$ ) and +LV  $dp/dt_{max}$  from 246±56 to 160±36 kPa·s<sup>-1</sup> ( $P<0.01$ ). Pd-Ia

increased mean CO, LVEDPS, and SV slightly ( $P>0.05$ ), Tab 1.

Dil 0.03–1 mg·kg<sup>-1</sup> produced increases in mean CBF, and dose-dependent decreases in SAP, MAP, +LV  $dp/dt_{max}$ , SVR, RPP and HR like the changes elicited by Pd-Ia except for an increase in HR. Although mean CO and SV were not changed markedly, Dil 1 mg·kg<sup>-1</sup> slightly decreased mean CO ( $P>0.05$ ). Judging from the dose-response relationships regarding MAP and RPP, the actions of Pd-Ia were approximately one-tenth as potent as those of Dil.

## DISCUSSION

In the present study, Pd-Ia caused an increase in CBF and decreases in MAP, +LV  $dp/dt_{max}$ , RPP and SVR. These cardiohemodynamic changes mean that Pd-Ia dilated coronary and peripheral arteries, reduced myocardial  $O_2$  consumption and depressed cardiac contractility, and they were similar to those induced by Dil except for a change in HR. Pd-Ia caused tachycardia whereas Dil produced bradycardia. We speculate that Pd-Ia exerts the cardiohemodynamic actions based on its Ca<sup>2+</sup> channel block action and has less inhibitory action on the automaticity of SA node and/or the atrioventricular conduction unlike Dil. In addition, another explanation may be reasonable; that is, if we select nifedipine (Nif) instead of Dil as a control drug for that a compensatory tachycardia induced by vasodilation of Nif is probably more potent than that of Dil, the actions of Pd-Ia on cardiovascular system seem to be near to those of Nif.

The Ca<sup>+</sup> antagonistic action of Pd-Ia has been shown to be the most potent in all of the components isolated from qian-hu<sup>(3,4)</sup>. The beneficial effects of Pd-Ia on cardiohemodynamics in anesthetized dogs suggest that this

**Tab 1. Maximal changes in cardiohemodynamics after iv Pd-Ia (n=7), diltiazem (n=6) and their respective solvents in anesthetized open-chest dogs.  $\bar{x} \pm s$ . <sup>a</sup>P>0.05, <sup>b</sup>P<0.05, <sup>c</sup>P<0.01 vs before drug.**

Drug	PEG	NS	Pd-Ia	Dil	Pd-Ia	Dil	Pd-Ia	Dil	Pd-Ia	Dil	Pd-Ia	Dil
Dose/mg·kg <sup>-1</sup>	Solvent		0.03		0.1		0.3		1.0		3.0	
mean CBF/ml·min <sup>-1</sup>												
B	25±11	22±10	—	20±5	25±11	20±7	26±11	22±10	25±11	23±10	25±11	—
A	28±13 <sup>a</sup>	23±10 <sup>a</sup>	—	27±5 <sup>b</sup>	24±11 <sup>a</sup>	32±5 <sup>c</sup>	28±11 <sup>a</sup>	36±10 <sup>b</sup>	38±11 <sup>b</sup>	36±10 <sup>b</sup>	58±16 <sup>c</sup>	—
SAP/kPa												
B	14±2	13±2	—	13±2	14±2	13±2	14±2	14±2	14±2	13±2	15±2	—
A	15±2 <sup>a</sup>	13±2 <sup>a</sup>	—	12±2 <sup>a</sup>	13±2 <sup>a</sup>	11±2 <sup>a</sup>	13±1 <sup>a</sup>	10±3 <sup>b</sup>	12±2 <sup>a</sup>	8±2 <sup>c</sup>	10±2 <sup>c</sup>	—
MAP/kPa												
B	12±2	11±1	—	12±2	12±2	12±2	12±2	11±2	12±2	10±1	13±2	—
A	13±2 <sup>a</sup>	11±2 <sup>a</sup>	—	10±2 <sup>a</sup>	12±2 <sup>a</sup>	10±2 <sup>a</sup>	11±2 <sup>a</sup>	8±2 <sup>b</sup>	10±1 <sup>b</sup>	6±2 <sup>c</sup>	8±1 <sup>c</sup>	—
LVEDP/kPa												
B	0.8±0.4	1.3±0.5	—	1.3±0.4	0.7±0.4	1.3±0.4	0.7±0.4	1.4±0.4	0.8±0.5	1.4±0.6	0.9±0.5	—
A	0.8±0.5 <sup>a</sup>	1.4±0.5 <sup>a</sup>	—	1.3±0.5 <sup>a</sup>	0.8±0.3 <sup>a</sup>	1.4±0.5 <sup>a</sup>	0.8±0.5 <sup>a</sup>	1.5±0.6 <sup>a</sup>	0.9±0.7 <sup>a</sup>	2.1±0.9 <sup>a</sup>	1.5±1.2 <sup>a</sup>	—
+LV dp/dt <sub>max</sub> /kPa·s <sup>-1</sup>												
B	237±54	212±25	—	239±22	239±56	234±18	239±52	233±26	236±52	227±28	246±56	—
A	246±56 <sup>a</sup>	213±26 <sup>a</sup>	—	232±26 <sup>a</sup>	233±50 <sup>a</sup>	218±21 <sup>a</sup>	224±44 <sup>a</sup>	193±22 <sup>b</sup>	198±39 <sup>b</sup>	124±25 <sup>c</sup>	160±36 <sup>c</sup>	—
mean CO/ml·min <sup>-1</sup>												
B	713±114	603±196	—	680±191	791±127	672±194	757±151	643±198	724±143	664±152	693±108	—
A	724±124 <sup>a</sup>	603±196 <sup>a</sup>	—	700±196 <sup>a</sup>	794±122 <sup>a</sup>	743±245 <sup>a</sup>	791±151 <sup>a</sup>	655±382 <sup>a</sup>	789±249 <sup>a</sup>	460±257 <sup>a</sup>	806±349 <sup>a</sup>	—
SV/ml·beat <sup>-1</sup>												
B	6.1±1.3	5.2±2.0	—	5.5±2.0	7.1±1.6	5.4±2.0	6.6±1.3	5.3±2.0	6.3±1.3	5.7±1.5	5.9±1.6	—
A	6.7±1.6 <sup>a</sup>	5.2±1.7 <sup>a</sup>	—	5.7±2.0 <sup>a</sup>	7.0±1.6 <sup>a</sup>	6.0±2.0 <sup>a</sup>	6.6±1.9 <sup>a</sup>	5.5±1.5 <sup>a</sup>	6.6±3.2 <sup>a</sup>	5.8±3.9 <sup>a</sup>	6.8±4.8 <sup>a</sup>	—
HR/bpm												
B	121±26	120±27	—	129±24	117±29	128±24	117±26	125±24	98±24	120±32	100±24	—
A	120±26 <sup>a</sup>	120±27 <sup>a</sup>	—	124±24 <sup>a</sup>	118±29 <sup>a</sup>	121±24 <sup>a</sup>	123±26 <sup>a</sup>	104±37 <sup>a</sup>	129±24 <sup>b</sup>	71±17 <sup>c</sup>	139±24 <sup>b</sup>	—
SVR/Pa·ml <sup>-1</sup> ·min <sup>-1</sup>												
B	19±4	20±9	—	19±9	15±4	20±3	16±4	20±3	17±4	16±3	19±4	—
A	17±4 <sup>a</sup>	20±9 <sup>a</sup>	—	17±9 <sup>a</sup>	15±4 <sup>a</sup>	15±3 <sup>a</sup>	15±4 <sup>a</sup>	15±3 <sup>b</sup>	13±4 <sup>a</sup>	11±3 <sup>b</sup>	12±7 <sup>b</sup>	—
RPP/MPa·bpm												
B	1.7±0.3	1.6±0.6	—	1.7±0.5	1.6±0.4	1.7±0.5	1.6±0.4	1.7±0.4	1.7±0.4	1.5±0.6	1.9±0.5	—
A	1.8±0.3 <sup>a</sup>	1.6±0.5 <sup>a</sup>	—	1.6±0.5 <sup>a</sup>	1.5±0.4 <sup>a</sup>	1.4±0.5 <sup>a</sup>	1.5±0.3 <sup>a</sup>	1.1±0.4 <sup>b</sup>	1.4±0.3 <sup>a</sup>	0.6±0.1 <sup>c</sup>	1.3±0.3 <sup>b</sup>	—

PEG: polyethylene glycol 200; NS: normal saline; Dil: diltiazem; B: before drug; A: after drug; CBF: coronary blood flow; SAP: systolic aortic pressure; MAP: mean aortic pressure; LVEDP: left ventricular end-diastolic pressure; +LV dp/dt<sub>max</sub>: maximal rate of rise in left ventricular blood pressure; CO: cardiac output; SV: stroke volume; SVR: systemic vascular resistance; RPP: rate pressure product; HR: heart rate.

novel agent isolated from a natural plant may be expected to become a suitable and versatile drug with lower-toxicity and higher-efficacy for the treatment of some cardiovascular, particularly ischemic heart diseases.

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 3'-当归酰氧基-4'-乙酰氧基-3', 4'-双氢邪蒿内酯对麻醉犬心脏血流动力学的影响

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**A 摘要** 本文研究了3'-当归酰氧基-4'-乙酰氧基-3', 4'-双氢邪蒿内酯(Pd-Ia)和地尔硫革(Dil)对麻醉犬心脏血流动力学的影响。Pd-Ia 剂量依赖性增加冠流量, 减少主动脉压(MAP), +dp/dt<sub>max</sub>, 率压积(RPP)及全身血管阻力, 并加快HR。Dil 与Pd-Ia 作用相似, 但明显减慢HR。Pd-Ia 对MAP及RPP的作用约为Dil的1/10。结果再次表明: Pd-Ia 是一Ca<sup>2+</sup>通道阻滞剂。

**关键词** 3'-当归酰氧基-4'-乙酰氧基-3', 4'-双氢邪蒿内酯; 香豆素类; 白花前胡; 血流动力学; 钙通道阻滞剂; 地尔硫革

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