

强心扩血管药羟苯氨酮对大鼠,猫和狗心脏血流动力学的影响

范礼理 孙丽红 李 娟

(中国医学科学院、中国协和医科大学药物研究所,北京 100050)

摘要 为了解强心扩血管新药羟苯氨酮(oxyphenamone, 9003)对在体心血管系统的效应,用多导生理仪与电磁流量计测定大鼠,猫与狗的血液流动力学参数。结果表明,静注羟苯氨酮引起血压与血管阻力中度下降,心输出量,心肌收缩力与收缩力变化速度,冠状动脉和股动脉血流量明显增加。羟苯氨酮对心率与左室压的影响呈现种系差别,它增加狗的左室收缩压与压力变化速度,降低左室舒张末期压力,小剂量羟苯氨酮(1 或 3 $\text{mg}\cdot\text{kg}^{-1}$)引起狗的心率轻度降低,剂量增到 6 $\text{mg}\cdot\text{kg}^{-1}$,心率中度加快。羟苯氨酮不影响猫的心率与左室压。大鼠静注羟苯氨酮后引起心率,左室收缩压与压力变化速度降低,左室舒张末期压力无变化。羟苯氨酮对心脏血流动力学的影响有待用病理模型作进一步观察。

关键词 强心扩血管药;羟苯氨酮;心脏血流动力学

强心与扩血管是治疗心力衰竭的主要措施。近廿年来发展的磷酸二酯酶抑制剂(PDEI)与多巴胺(DA)类药物兼具强心扩血管作用,治疗指数比强心甙宽,为心衰的治疗增添新的工具^[1~4]。由于它们的正性肌力作用机制最终是通过增加细胞内钙离子,不免有增加心率或致心律失常的副作用,限制其发展与应用。通过增加收缩蛋白对 Ca^{2+} 的敏感性从而增加心肌收缩力是引起正性肌力作用的另一途径。已发现的药物有 pimobendan^[5], MCl-154^[6], EMD 53998^[7] 等,归纳为“钙增敏剂”。临床试验对心力衰竭有治疗作用,但是尚未广泛使用。

在寻找治疗心血管病的药物研究中,发现氨基酮类化合物羟苯氨酮有明显的强心扩血管作用^[8]。体外实验显示它有正性肌力,负性频率和松弛血管平滑肌的作用^[9]。其强心作用机制与强心甙,儿茶酚胺或 PDEI 不同,它主要通过增加收缩蛋白对 Ca^{2+} 的敏感性^[10,11],属于一种新的“钙增敏剂”。因此,有必要研究它

对在体心血管系统的作用。本文报道羟苯氨酮对正常大鼠、猫与狗心脏血流动力学的影响。

材 料 与 方 法

雄性 Wistar 种大鼠,(体重 242 ± 24 g)。猫(3.1 ± 0.7 kg)与狗(14.7 ± 2.8 kg)均为杂种,♀♂各半。给予戊巴比妥钠麻醉(大鼠与猫 $40 \sim 50$ $\text{mg}\cdot\text{kg}^{-1}$ ip,狗 30 $\text{mg}\cdot\text{kg}^{-1}$ iv)。气管插管,人工呼吸,监测动脉压(MAP)与心电图。将 PE-50 导管从大鼠右颈动脉插入左心室,测左室压及其压力变化速度($\pm dP/dt_{\max}$)。猫与狗作左侧开胸,从心尖插导管至左心室测压。将 Waltan-Brodie 应变弓植入猫与狗的左心室前壁(猫用 XH-1 型,北京航天医学工程研究所;狗用 TH-602 T 型,日本光电公司),测定心肌节段性收缩与收缩力变化速度($\pm dT/dt_{\max}$)。用电磁流量计(MFV-3200 型,日本光电公司)测定狗的升主动脉,冠状动脉,颈内动脉,股动脉与猫的颈总动脉和股动脉血流量。以升主动脉流量作为心输出量(CO),按公式计算心脏指数(CI),左心作功(LVW),总外周血管阻力(SVR)与各动脉的血管阻力^[12]。各项参数记

录于 RM-86 型(日本光电公司)生理记录仪。实验数据用 $\bar{x} \pm s$ 表示。用 t 测验判断组间或给药前后的差别显著性。

羟苯氨酮系白色结晶,纯度为 $99 \pm 0.5\%$ 。配制时先用丙二醇(终浓度 $5 \sim 10 \text{ ml}\%$)溶解,再加生理盐水稀释成 $1 \sim 5 \text{ mg} \cdot \text{ml}^{-1}$ 。iv 的剂量为:狗 $0.5, 1, 3, 6 \text{ mg} \cdot \text{kg}^{-1}$,猫 $2, 4, 8 \text{ mg} \cdot \text{kg}^{-1}$,大鼠 $3, 6, 10 \text{ mg} \cdot \text{kg}^{-1}$ 。注射速度为 $1 \sim 4 \text{ min}$,二次给药间隔时间为 $30 \sim 60 \text{ min}$ 。

动脉注射的剂量为 $0.1 \sim 0.2 \text{ mg} \cdot \text{kg}^{-1}$,二次给药间隔时间为 $15 \sim 20 \text{ min}$ 。

结 果

表 1 与 2 是本研究中麻醉大鼠,猫与狗心脏血流动力学参数的基础值。iv 羟苯氨酮后立即引起反应, $4 \sim 6 \text{ min}$ 达峰值,作用维持 $15 \sim 30 \text{ min}$ 。iv 溶剂对各项参数无明显影响。

Tab 1 Cardiac hemodynamic variables before medication in anesthetized rats, cats and dogs

Parameter	Dog ($n = 16$)	Cat ($n = 20$)	Rat ($n = 18$)
HR ($\text{beat} \cdot \text{min}^{-1}$)	162 ± 26	156 ± 32	349 ± 28
MAP (kPa)	15.87 ± 2.93	13.07 ± 2.80	16.67 ± 3.07
LVSP (kPa)	19.87 ± 2.67	17.47 ± 3.87	23.47 ± 0.93
LVEDP (kPa)	0.56 ± 0.40	0.25 ± 0.25	0.20 ± 0.33
$+dP/dt_{\max}$ ($\text{kPa} \cdot \text{s}^{-1}$)	521 ± 160	703 ± 282	1147 ± 256
$-dP/dt_{\max}$ ($\text{kPa} \cdot \text{s}^{-1}$)	417 ± 194	363 ± 175	791 ± 201

$\bar{x} \pm s$. HR: Heart rate; MAP: Mean arterial pressure; LVSP: Left ventricular systolic pressure; LVEDP: Left ventricular end diastolic pressure; $+dP/dt_{\max}$: The maximum rise rate of left ventricular pressure; $-dP/dt_{\max}$: The maximum decline rate of left ventricular pressure.

Tab 2 Cardiac hemodynamic variables before medication in anesthetized cats and dogs

Parameter	Dog ($n = 12$)	Cat ($n = 8$)
Contractile force (g)	58 ± 22	80 ± 15
$+dT/dt_{\max}$ ($\text{g} \cdot \text{s}^{-1}$)	153 ± 31	384 ± 73
$-dT/dt_{\max}$ ($\text{g} \cdot \text{s}^{-1}$)	183 ± 46	288 ± 58
CI ($\text{L} \cdot \text{min}^{-1} / \text{m}^2$)	2.54 ± 1.55	
LVW ($\text{kg} \cdot \text{m} \cdot \text{min}^{-1}$)	2.54 ± 1.29	
SVR ($\text{kPa} \cdot \text{L} \cdot \text{min} \cdot \text{kg}^{-1}$)	0.79 ± 0.25	
FBF ($\text{ml} \cdot \text{min}^{-1}$)	11.4 ± 8.1	6.0 ± 3.0
FVR ($\text{kPa} \cdot \text{ml} \cdot \text{min}^{-1}$)	1.49 ± 0.76	5.94 ± 3.31
ICBF ($\text{ml} \cdot \text{min} \cdot 100 \text{ g}^{-1}$)	81.6 ± 39.7	23.1 ± 9.2
ICVR ($\text{kPa} \cdot \text{ml} \cdot \text{min} \cdot 100 \text{ g}^{-1}$)	0.26 ± 0.14	0.73 ± 0.39
CBF ($\text{ml} \cdot \text{min} \cdot 100 \text{ g}^{-1}$)	91.3 ± 38.7	
CVR ($\text{kPa} \cdot \text{ml} \cdot \text{min} \cdot 100 \text{ g}^{-1}$)	0.20 ± 0.08	

$\bar{x} \pm s$. $+dT/dt_{\max}$: The maximum rise rate of contractile force; $-dT/dt_{\max}$: The maximum decline rate of contractile force; CI: Cardiac index; LVW: Left ventricular work; SVR: Systemic vascular resistance; FBF: Blood flow of femoral artery; FVR: Vascular resistance of femoral artery; ICBF: Blood flow of internal carotid artery in dogs or blood flow of common carotid artery in cats; ICVR: Vascular resistance of internal carotid artery in dogs or vascular resistance of common carotid artery in cats; CBF: Blood flow of coronary artery; CVR: Vascular resistance of coronary artery.

1 羟苯氨酮对动物血压、心率与心电图的影响

iv 羟苯氨酮 $1 \sim 10 \text{ mg} \cdot \text{kg}^{-1}$ 引起 MAP 中度下降。随药物剂量的增加,作用强度增加,时间延长(20~60 min)。给药后大鼠($3 \sim 10 \text{ mg} \cdot \text{kg}^{-1}$)、猫($2 \sim 8 \text{ mg} \cdot \text{kg}^{-1}$)与狗($0.5 \sim 6 \text{ mg} \cdot \text{kg}^{-1}$)的 MAP 较给药前分别下降 21%~38%, 12%~19% 与 6%~19%。

iv 羟苯氨酮引起大鼠心率(HR)减少 $5.9 \pm 3.9\%$ ($P < 0.05$, $n = 6$)。它对猫的 HR 无明显影响。低剂量羟苯氨酮(1 与 $3 \text{ mg} \cdot \text{kg}^{-1}$)引起狗的 HR 轻度降低($-3.3 \pm 3.1\%$, $P < 0.01$ 与 $-5.8 \pm 6.4\%$, $P < 0.01$), 剂量增加到 $6 \text{ mg} \cdot \text{kg}^{-1}$ ($n = 7$), 引起 HR 比给药前最大增加 $22.1 \pm 11.7\%$ ($P < 0.001$) (图 1)。iv 羟苯氨酮对大鼠, 猫与狗的心电图波形均无明显影响。

2 羟苯氨酮对左室压的影响

给大鼠 iv 羟苯氨酮 $3 \sim 10 \text{ mg} \cdot \text{kg}^{-1}$ 引起左室收缩压(LVSP)减少 7~19%, $\pm dP/dt_{\max}$ 减少 14~29%, 对左室舒张末期压力(LVEDP)影响不明显。羟苯氨酮不影响猫的左室压。它明显增加狗的 LVSP 与 $\pm dP/dt_{\max}$, 并减少 LVEDP。iv $6 \text{ mg} \cdot \text{kg}^{-1}$ ($n = 7$) 后, LVSP 比给药前最大增加 $40.3 \pm 26.4\%$ ($P < 0.01$),

$\pm dP/dt_{\max}$ 分别增加 $67.1 \pm 30.9\%$ ($P < 0.001$) 与 $38.9 \pm 36.3\%$ ($P < 0.05$), LVEDP 最低减少 $19.5 \pm 18.7\%$ ($P < 0.05$, 见图 2)。

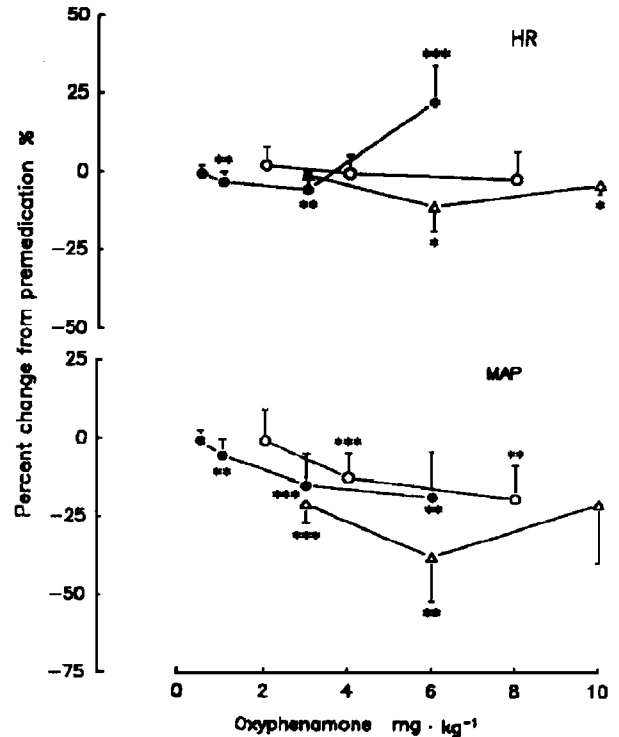


Fig 1 Maximum effect of oxyphenamone on heart rate (HR) and mean arterial pressure (MAP) in anesthetized normal animals. $\triangle - \triangle$ Rats, $n = 5 \sim 6$; $\circ - \circ$ Cats, $n = 5 \sim 8$; $\bullet - \bullet$ Dogs, $n = 6 \sim 11$. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs premedication.

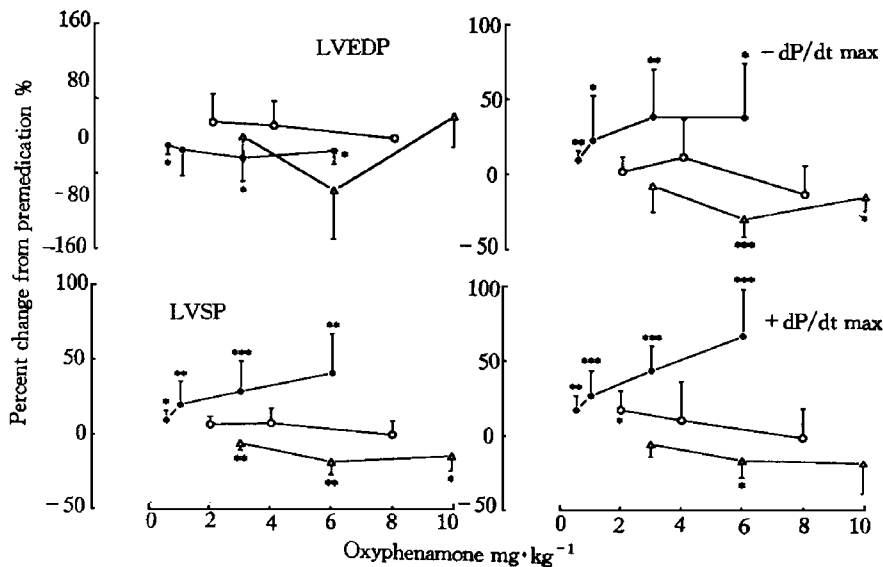


Fig 2 Maximum effect of oxyphenamone on left ventricular systolic pressure (LVSP), left ventricular end diastolic pressure (LVEDP) and $\pm dP/dt_{\max}$ in anesthetized normal animals. $\triangle - \triangle$ Rats, $n = 5 \sim 6$; $\circ - \circ$ Cats, $n = 5 \sim 8$; $\bullet - \bullet$ Dogs, $n = 6 \sim 9$. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs premedication.

3 羟苯氨酮对心肌收缩力的影响

羟苯氨酮能剂量依赖性地明显增加猫与狗的心肌收缩力。给狗 iv 0.5 mg·kg⁻¹ (n = 6) 即引起心肌收缩力增加 7.9 ± 5.6% (P < 0.01), ±dT/dt_{max} 分别增加 12.6 ± 3.7% (P < 0.01) 与 30.4 ± 17.2% (P < 0.05)。剂量为 6 mg·kg⁻¹ (n = 6) 时, 心肌收缩力增加 49.9 ± 17.9% (P < 0.01), +dT/dt_{max} 增加 42.2 ± 22.1% (P < 0.05)。羟苯氨酮增加猫心肌收缩力与 ±dT/dt_{max} 的反应与狗相似。(图 3, 4)

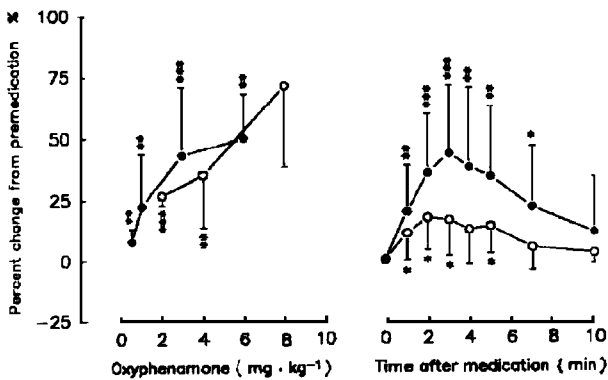


Fig 3 Effect of oxyphenamone on myocardial contractile force. Left: maximum responses to dogs (●—●, n = 6~9) and cats (○—○, n = 4~6). Right: time course produced by oxyphenamone at 3 mg·kg⁻¹ iv to dogs (●—●, n = 9) and 4 mg·kg⁻¹ to cats (○—○, n = 6) are showed on the left. * P < 0.05, ** P < 0.01, *** P < 0.001 vs premedication.

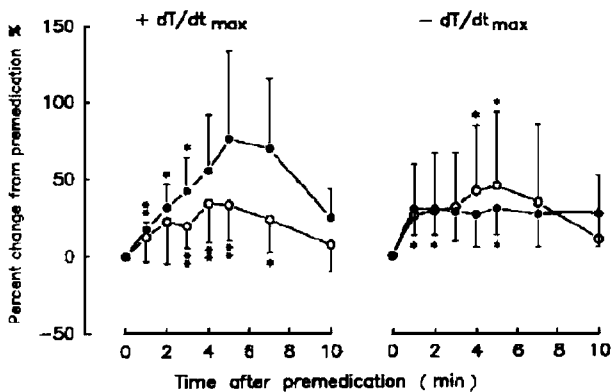


Fig 4 The time course of ±dT/dt_{max} after iv of oxyphenamone. ●—● 6 mg·kg⁻¹ in dogs, n = 3; ○—○ 8 mg·kg⁻¹ in cats, n = 6. * P < 0.05, ** P < 0.01, *** P < 0.001 vs premedication.

4 羟苯氨酮对心输出量, 左心做功与总外周血管阻力的影响

羟苯氨酮 1 (n = 6), 3 (n = 6) 或 6 (n = 7) mg·kg⁻¹ iv 后, 引起狗的心脏指数(CI)分别比

给药前增加 13.2 ± 8.2% (P < 0.01), 25.7 ± 11.5% (P < 0.05) 和 18.5 ± 10.6% (P < 0.001)。它不影响左心做功(LVW)。给药后总外周血管阻力(SVR)分别减少 15.8 ± 4.6% (P < 0.001), 29.6 ± 12.9% (P < 0.001) 与 26.4 ± 10.3% (P < 0.001)。

5 对动脉血流量的影响

给狗股动脉内注射羟苯氨酮 0.1~0.2 mg·kg⁻¹, 引起股动脉血流量增加 74 ± 35%~93 ± 43%, 血管阻力明显下降。若将药物注入狗的颈内动脉, 则不影响其流量和血管阻力。

iv 羟苯氨酮引起猫与狗的股动脉血流量剂量依赖性地增加 28%~65%, 股动脉血管阻力减少 20%~47%。羟苯氨酮 6 mg·kg⁻¹ (n = 7) 能使狗的冠状动脉流量最大增加 40.1 ± 12.1% (P < 0.001), 冠脉血管阻力减少 37.2 ± 5.6% (P < 0.001)。(图 5)。iv 羟苯氨酮不影响狗的颈内动脉与猫的颈总动脉血流量。显示不同血管对羟苯氨酮的反应不同。

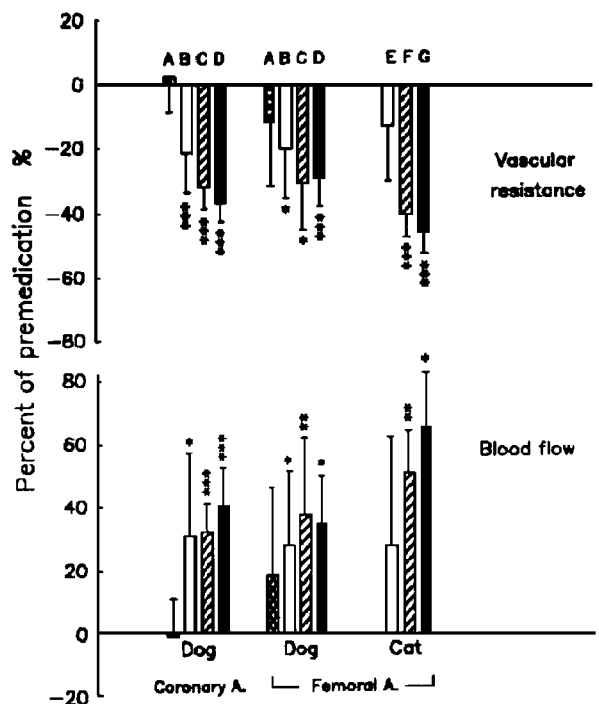


Fig 5 Maximum effects of oxyphenamone on blood flow and vascular resistance in coronary and femoral arteries. A, B, C, D: oxyphenamone 0.5, 1, 3, 6 mg·kg⁻¹, respectively in dog coronary arteries (n = 5~7) and dog femoral arteries (n = 5~6). E, F, G: oxyphenamone 2, 4, 8 mg·kg⁻¹, respectively in cat femoral arteries, n = 3. * P < 0.05, ** P < 0.01, *** P < 0.001 vs premedication.

讨 论

发展兼具强心与扩血管作用,又不影响心率或心律的药物用于治疗心力衰竭是人们的期望^[13]。羟苯氨酮是氨基酮类新化合物。本研究显示 iv 羟苯氨酮能降低实验动物的血压与 LVEDP,增加动脉血流量,减少血管阻力。表明它有扩张在体血管,降低心脏负荷的作用。羟苯氨酮增加猫与狗的心肌收缩力, $\pm dT/dt_{\max}$, CI, LVSP 与 $\pm dP/dt_{\max}$, 表明它有改善在体心脏泵功能的作用。这些反应与它在离体心肌或血管的表现一致。表明羟苯氨酮兼具强心扩血管作用,将有利于心衰的治疗。

然而,羟苯氨酮不影响正常猫的 LVP。它对大鼠 LVP 的影响与对狗的相反,即减低大鼠的 LVSP 与 $\pm dP/dt_{\max}$ 。此差别可能与心肌收缩成分的种系差异有关。在 PDEI 类强心药的药理作用中也发现类似现象^[14]。因此,为研究新型强心扩血管剂的作用,宜用多种系动物作观察,尤其是需要用心力衰竭等病理模型进一步评价其作用。

羟苯氨酮的毒性较低。小鼠 iv 羟苯氨酮的 LD₅₀ 为 $107 \pm 10 \text{ mg} \cdot \text{kg}^{-1}$ 。它对狗强心扩血管作用的最小有效量为 $0.5 \text{ mg} \cdot \text{kg}^{-1}$ 。可见羟苯氨酮的治疗指数比强心甙宽^[15]。羟苯氨酮不引起快速型室性心律失常,它只轻度影响心率,而且随剂量或动物种系的差别而不同,提示其作用性质不同于儿茶酚胺或 PDEI,可能更有利于心血管病的治疗,待用心力衰竭或心肌缺血等病理模型作研究,以确定其作用意义。

致谢 邹强参加部分实验。

参 考 文 献

- 1 Alousi AA, Farah AE, Leshner GY, *et al.* Cardiotoxic activity of amrinone — Win 40680 [5-Amino-3, 4'-bipyridin-6(1H)-one]. *Circ Res*, 1979, **45**:666
- 2 Alousi AA, Canter JM, Montenegro MJ, *et al.* Cardiotoxic activity of milrinone, a new

- and potent cardiac bipyridin, on the normal and failing heart of experimental animals. *J Cardiovasc Pharmacol*, 1983, **5**:792
- 3 Cargnelli G, Piovan D, Bova S, *et al.* Present and future trends in research and clinical applications of inodilators. *J Cardiovasc Pharmacol*, 1989, **14**(Suppl 8): S124
- 4 Cas LD, Metra M, Visioli O. Clinical pharmacology of inodilators. *J Cardiovasc Pharmacol*, 1989, **14**(suppl. 8):S60
- 5 Verdouw PD, Hartog JM, Duncker DJ, *et al.* Cardiovascular profile of pimobendan, a benzimidazole-pyridazinone derivative with vasodilating and inotropic properties. *Eur J Pharmacol*, 1986, **126**:21
- 6 Narimatsu A, Kitada Y, Satoh N, *et al.* *In vitro* characterization of the effects of MCI-154, a novel cardiotoxic agent, on cardiac tissues. *Jpn J Pharmacol*, 1989, **49**:397
- 7 Beier N, Harting J, Jonas R, *et al.* The novel cardiotoxic agent EMD 53998 is a potent "Calcium sensitizer". *J Cardiovasc Pharmacol*, 1991, **18**:17
- 8 邵国贤, 范礼理, 莫若莹, 等. 氨基酮类化合物的制备方法. 发明专利公报, 1991, **7**(8):27
- 9 范礼理, 孙丽红, 林勇. 强心扩血管药羟苯氨酮对离体心肌与血管的作用. 药学报, 1997, (待发表):
- 10 范礼理. 收缩蛋白对 Ca²⁺ 的敏感性与钙增敏剂的研究. 见: 陈维洲等主编. 心血管药理学进展. 北京: 人民卫生出版社, 1995:251~263
- 11 滕健, 范礼理. 新型强心药氨基酮类化合物对心肌细胞内 [Ca²⁺] 与 "钙敏感性" 的影响. 中国病理生理杂志, 1996, **12**:733
- 12 范礼理, O'keefe DD, Powell WJ. 葛根素对急性心肌缺血狗区域性心肌血流与心脏血流动力学的作用. 药学报, 1984, **19**:801
- 13 Godfrained T. Comparative pharmacology of cardiac and vascular tissues in heart failure.

- J Cardiovasc Pharmacol*, 1989, **14**(Suppl. 8): S1
- 14 Alousi AA, Stankus GP, Stuart JC, *et al.* Characterization of the cardiotoxic effects of milrinone, a new and potent cardiac bipyridine, on isolated tissues from several animal species. *J Cardiovasc Pharmacol*, 1983, **5**:804
- 15 高世嘉, 曾贵云. 黄花夹竹桃次甙甲和次甙乙的强心作用与毒性. 药理学报, 1983, **18**:572

EFFECT OF OXYPHENAMONE, A NEW INODILATOR, ON CARDIAC HEMODYNAMICS IN NORMAL RAT, CAT AND DOG

LL Fan, LH Sun and J Li

(*Department of Pharmacology, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050*)

ABSTRACT For studying the cardiotoxic and vasodilating effect of oxyphenamone *in vivo*, cardiac hemodynamic variables of anesthetized normal rats, cats and dogs were determined with a polygraph and electromagnetic flowmeters. Intravenous injection of oxyphenamone ($0.5 \sim 10 \text{ mg} \cdot \text{kg}^{-1}$) dose-dependently decreased the mean arterial pressure and systemic vascular resistance moderately and increased cardiac output, myocardial contractile force and $\pm dT/dt_{\text{max}}$. The blood flow of coronary and femoral arteries increased markedly and their vascular resistance decreased but the blood flow and vascular resistance of cerebral artery did not change. Some species differences were observed in the effect of oxyphenamone on heart rate (HR) and left ventricular pressure (LVP). Oxyphenamone did not influence the HR and LVP in normal cats. It decreased the HR, left ventricular systolic pressure (LVSP) and $\pm dP/dt_{\text{max}}$, while did not affect the left ventricular end diastolic pressure (LVEDP) in rats. In contrast, administration of oxyphenamone to dogs increased LVSP and $\pm dP/dt_{\text{max}}$ markedly and diminished LVEDP slightly. Oxyphenamone decreased HR slightly at lower dosage (1 and $3 \text{ mg} \cdot \text{kg}^{-1}$), but increased heart rate moderately at high dose ($6 \text{ mg} \cdot \text{kg}^{-1}$) in dogs. These indicate that oxyphenamone has cardiotoxic and vasodilating effects *in vivo*. Whether the effects of oxyphenamone on cardiac hemodynamics would be useful for the treatment of heart failure should be evaluated further.

KEY WORDS Oxyphenamone; Cardiotoxic agents; Vasodilator agents; Inodilators; Cardiac hemodynamics