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氧苦参碱对心肌梗死犬心律失常的作用

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 R 972.2

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Effects of oxymatrine on arrhythmia in dogs with myocardial infarction

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KEY WORDS oxymatrine; myocardial infarction; arrhythmia

AIM: To study the effects of oxymatrine (Oxy) on arrhythmia in dogs with myocardial infarction.

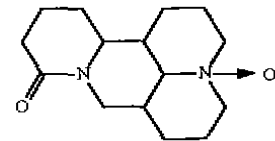
METHODS: Partly ligating the left anterior descending coronary artery in the open-chest dogs produced myocardial infarction of left anterior ventricular wall. After 5-8 d, the diastolic excitability threshold (DET), the effective refractory periods (ERP) and arrhythmias were determined by programmed electric stimulation (PES). **RESULTS:** Oxy (iv 50 mg·kg⁻¹) increased DET from 2.53±1.28 to 3.19±1.62 V, lengthened ERP from 182±25 to 219±43 ms at normal region and from 206±49 to 235±55 ms at infarct region in left ventricle, but had no effects on dispersion of ERP, QTc interval and ventricular tachycardia (VT) or ventricular fibrillation (VF). Procainamide (Pro) (iv 25 mg·kg⁻¹) increased DET and lengthened ERP and QTc interval, but decreased the dispersion of ERP. Pro prevented PES-induced VT/VF and spontaneous ischemia-related VF. **CONCLUSION:** The increased DET and lengthened ERP of Oxy are its anti-arrhythmic mechanism.

关键词 氧苦参碱; 心肌梗死; 心律失常

目的: 研究氧苦参碱对心肌梗死犬心律失常的作用。 **方法:** 部分结扎犬左冠状动脉前降支, 造成

前壁心肌梗死, 5-8 d 后, 使用程控电刺激技术 (PES), 测定心肌舒张期兴奋阈值 (DET) 和有效不应期 (ERP), 并诱发心律失常, 然后造成冠状动脉左旋支急性栓塞, 观察室颤发生。 **结果:** Oxy (iv 50 mg·kg⁻¹) 明显提高 DET (由 2.53±1.28 至 3.19±1.62 V), 延长左室正常区 ERP (由 182±25 至 219±43 ms) 及梗塞区 ERP (由 206±49 至 235±55 ms), 但对 ERP 离散性, QTc 间期及 VT/VF 无影响; Pro (iv 25 mg·kg⁻¹) 则能提高 DET, 延长 ERP 及 QTc 间期, 缩小 ERP 离散性, 预防 PES 诱发的 VT/VF 及再缺血所致 VF。 **结论:** Oxy 提高 DET, 延长 ERP 是其抗心律失常的机制

氧苦参碱 (oxymatrine) (Oxy) 是苦参, 苦豆子和山豆根等植物所含的生物碱^[1-3]。



Oxymatrine

Oxy 能对抗实验性心律失常^[1,4], 且对临床室性, 室上性快速心律失常有治疗作用^[5]。临床上, 心肌梗死与心律失常发生关系密切^[6]。本文探讨了 Oxy 抗心律失常的作用机制。

MATERIALS AND METHODS

1 药品 Oxy 由宁夏盐池制药厂提供, 为淡黄色粉末, 纯度为 96.5%, 本院制剂室制成 4% 的注射液。普鲁卡因胺 (Pro) 注射液 (0.1 kg·L⁻¹) 由上海医科大学红旗制药厂生产。

2 心肌梗死 杂种犬 19 只, ♀♂不拘, 体重 13.3±s 1.8 kg, 麻醉后人工呼吸, 经左第 5 肋间开胸, 用左前降支 + 吻合支二期结扎法造成左室前壁心肌梗死^[7,8]。

3 梗死后的左室程控刺激 PES^[7,8] 术后 5-8 d, 将犬重新麻醉, 人工呼吸, 暴露心脏, 维持动脉血 pO₂ 为 10.5-15 kPa, pCO₂ 为 4.5-6 kPa, pH 7.35-7.45。室内温度 0-5℃, 电热毯加温维持肛温 38.2-39.2℃。将

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前端带有小钩直径 0.2 mm 的单极心肌电极插入左室梗死区, 正常区和右室心肌. 采用国产 XD-2A 型心脏电生理诊疗仪行心室 PES, 电流强度为 2 倍舒张期兴奋阈值, 脉宽 2 ms, 以国产 SJ-41 型多道生理记录仪记录心电.

3.1 测定心室舒张期兴奋阈值(DET) 心室基础刺激间期(S₁-S₁)为 300 ms, 逐步增加电压, 直至引起 8 个以上心室搏动, 所需的最小电压定为 DET.

3.2 测定心室有效不应期(ERP)和左室 ERP 离散性(VDR) 即左室最长与最短 ERP 的差值, 左室正常区 ERP 离散性(NDR, 即左室正常区最长与最短 ERP 的差值). 左室梗死区 ERP 离散性(IDR, 即左室梗死区最长与最短 ERP 的差值).

3.3 诱发与终止心律失常 在梗死区边缘选 4-6 个部位, 以 S₁-S₁ 为 300 ms, 在每 8 个 S₁ 之后, 给予 2 个(S₂, S₃)期前刺激, 每个期前刺激分别按 10 ms 步长进行负扫描, 直达不应期. PES 终点为诱发室性心动过速(VT)或室颤(VF)或是完成整个刺激程序.

PES 诱发的室性心律失常类型为: (1) VT: QRS 波群形态基本一致, 周长 > 120 ms, 持续 ≥ 30 s 为持续性 VT (SVT); 连续至少 6 个心室搏动并于 30 s 内自动终止者为非持续性 VT (NVT). (2) VF: QRS 波群形态, 节律紊乱者. (3) 反复心室搏动(RVR): 室性搏动 2-5 个.

诱发的 SVT 用心室短程快速刺激终止; 诱发的 VF 经心外膜除颤, 功率 15-20 J.

犬分 3 组: NS 空白对照组 6 只(iv NS 2.5 mL·kg⁻¹), Oxy 组 7 只(iv Oxy 50 mg·kg⁻¹), Pro 组 6 只(iv Pro 25 mg·kg⁻¹), 于给药前后进行 PES, 刺激部位与程序不变.

4 梗死后再缺血引发 VF⁽⁷⁾ 实验结束时, 在距起源 1 cm 处, 分离左旋支(LCX), 并插入前端 4 mm 未绝缘的针形电极, 输入 150 μA 直流电, 持续监护心电至犬出现 VF 或通电 6 h 止.

5 病理检查⁽⁸⁾ 剖开 LCX, 证实 LCX 内血栓形成, 平行房室沟作厚约 5 mm 的心肌连续切片, 氯化三苯基四氮唑(TTC)染色. 观察前壁心肌梗死的部位及形态并确定电极位置, 切出梗死心肌称重.

RESULTS

1 对 QTc 间期的影响 Oxy iv 前后, II 导联 QTc 间期分别为 388 ± 68 和 424 ± 55 ms (n = 7, P > 0.05). iv Pro 前后, QTc 从 410 ± 50 延长至 510 ± 50 ms (n = 6, P < 0.01), 两组比较, 差异显著(P < 0.05). 对照组 iv NS 前后, QTc 分别为 398 ± 48 和 408 ± 58 ms (n = 6, P > 0.05). 对照组与 Oxy 组比较, 无显著差异(P > 0.05); 与 Pro 组比较, 差异显著(P < 0.05).

2 对左室 DET 的影响 左心室多部位测定表明, Oxy 能明显提高 DET, iv Oxy 后, 左室 DET 由 2.53 ± 1.28 提高到 3.19 ± 1.62 V (n = 47, P < 0.01, n 为测定位点数之和). 其中左室正常区由 2.25 ± 0.76 提高到 2.99 ± 1.44 V (n = 24, P < 0.05); 但梗死区 DET 分别为 2.93 ± 1.62 和 3.51 ± 1.80 V (n = 23, P > 0.05). iv Pro 后, 正常区 DET 从 1.3 ± 0.6 增到 1.5 ± 0.6 V (n = 9, P < 0.05); 梗死区 DET 从 3.0 ± 2.8 V 增至 4 ± 3 V (n = 31, P < 0.01). NS 组对正常区和梗死区无明显影响.

3 对心室 ERP 和 ERP 离散性的影响 Oxy 和 Pro iv 后, 右室有效不应期(RERP), 左室正常区有效不应期(NERP)及左室梗死区有效不应期(IERP)均显著延长, 且 Oxy 延长 NERP 作用较 Pro 更明显(Tab 1). Oxy 似有增大 NDR, IDR 和 VDR 的作用, 但统计学上无显著差异; Pro 则能缩小 IDR, VDR (Tab 2).

Tab 1. Effects of iv oxymatrine (50 mg·kg⁻¹) and procainamide (25 mg·kg⁻¹) on effective refractory period (ERP) of right ventricle (RERP), normal region (NERP) and infarct region (IERP) in left ventricle in dogs with myocardial infarction. $\bar{x} \pm s$. *paired t test. ^aP > 0.05, ^bP < 0.05, ^cP < 0.01 vs before. ^dP > 0.05, ^eP < 0.05, ^fP < 0.01 vs Oxy.

Groups	ERP/ms	Sites	Before	After	Increase/%
NS	RERP	5	158 ± 22	162 ± 16 ^a	3 ± 1 ^f
	NERP	20	162 ± 20	162 ± 18 ^a	0 ^f
	IERP	24	188 ± 23	186 ± 25 ^a	-1 ± 1 ^f
Oxy	RERP	9	174 ± 24	210 ± 40 ^{c*}	20 ± 10
	NERP	24	182 ± 25	219 ± 43 ^{c*}	20 ± 13
	IERP	21	206 ± 49	235 ± 55 ^{c*}	14 ± 9
Pro	RERP	5	170 ± 30	184 ± 24 ^b	10 ± 6 ^d
	NERP	19	165 ± 26	192 ± 23 ^b	13 ± 4 ^d
	IERP	27	180 ± 30	210 ± 30 ^b	13 ± 7 ^d

4 对 PES 诱发的 VT/VF 的影响 Oxy iv 和 NS 对 PES 诱发的 VT/VF 无明显影响; 而 Pro 则能显著减少 PES 诱发的 VT/VF (Tab 3).

5 对左室后侧壁缺血所致自发性 VF 的影响 LCX 通电后, 三组犬均在基本相同的时间内出现由后侧壁缺血引起的 ECG: ST_{II, III, avL, avF} 抬高, 除 Pro 组 3 只犬外, 其他犬均在 ST 抬高后 30 min 内出现自发性 VF, 3 组间差异不显著(Tab 4).

Tab 2. Effects of iv oxymatrine 50 mg · kg⁻¹ and procainamide 25 mg · kg⁻¹ on dispersion of refractoriness (DR) within normal region (NDR), infarct region (IDR) and left ventricle (VDR) in dogs with myocardial infarction. $\bar{x} \pm s$. ^b*P* < 0.05. ^c*P* < 0.01 vs before.

Groups	Dispersion of ERP/ms	Dogs	Before	After
NS	NDR	6	12 ± 9	14 ± 5 ^b
	IDR	6	34 ± 24	42 ± 17 ^b
	VDR	6	48 ± 17	52 ± 14 ^b
Oxy	NDR	5	17 ± 12	40 ± 42 ^b
	IDR	5	28 ± 19	38 ± 20 ^b
	VDR	6	43 ± 14	61 ± 26 ^b
Pro	NDR	6	15 ± 5	12 ± 6 ^b
	IDR	6	14 ± 15	28 ± 14 ^c
	VDR	6	48 ± 13	35 ± 15 ^c

Tab 3. Effects of iv Oxy 50 mg · kg⁻¹ and Pro 25 mg · kg⁻¹ on ventricular tachycardia or fibrillation by programmed electric stimulation in dogs with myocardial infarction. Exact probabilities in 2 × 2 table was used. *n*₁ or *n*₂ = number of dogs with VT or VF in total number (*n*) of dogs. ^a*P* > 0.05. ^b*P* < 0.05 vs control. ^d*P* > 0.05. ^e*P* < 0.05 vs before medication.

Groups	Before medication <i>n</i> ₁ / <i>n</i>	After medication <i>n</i> ₂ / <i>n</i>
Oxy	6/7 ^a	5/7 ^{cd}
Pro	6/6 ^a	1/6 ^{be}
NS	6/6	6/6 ^c

Tab 4. Effects of iv Oxy 50 mg · kg⁻¹ on acute posterolateral ischemia and spontaneous ventricular fibrillation in dogs with myocardial infarction. *n*₁ = number of dogs with VT or VF. *n* = total dogs. $\bar{x} \pm s$. ^a*P* > 0.05 vs saline.

Groups	Time to ST-segment elevation/min	Infarct size/%	Spontaneous VF (<i>n</i> ₁ / <i>n</i>)
Oxy	123 ± 33 ^a	34 ± 6 ^a	5/5 ^a
Pro	110 ± 40 ^a	32 ± 7 ^a	2/5 ^a
NS	104 ± 30	31 ± 8	5/5

6 病理检查 自发性 VF 或通电 6 h 处死犬后, Oxy 组 (*n* = 5), Pro 组 (*n* = 5) 和 NS 组 (*n* = 5) 犬, 均证实有 LCX 内血栓形成, 三组犬之间梗死范围大小相似 (Tab 4). (Oxy 组 2 只犬, Pro 组和 NS 组各一只犬, PES 诱发 VF 经直流电除颤不

能复律死亡, 剔除于本研究).

DISCUSSION

本实验证实了 Oxy 能明显提高 DET, 明显延长 ERP, 前者能降低心肌细胞自律性, 减少触发活动发生^[9], 后者可能使折返落入有效不应期而终止心律失常^[8]. 因此, Oxy 提高 DET, 延长 ERP, 是其抗心律失常作用机制. 这对已经报道的文献结果^[1,4,5]作出了合理解释, 也为 Oxy 临床应用提供了理论指导.

ERP 离散度越大, 室颤阈越低, PES 越易诱发 VT/VF^[10], 由于 Oxy 对左室 ERP 离散度无明显影响, 故不能有效地预防 PES 诱发的 VT/VF; Pro 由于缩短 ERP, 故能有效地预防 PES 诱发的 VT/VF. LCX 急性栓塞时, 左室缺血和梗死面积扩大, 易致室颤发生^[11]. Oxy 通过提高 DET 而升高室颤阈, 但由于其不能缩小 ERP 离散度, 使其抗室颤作用受到一定程度限制, Pro 通过提高 DET 和缩小 ERP 离散度而具有抗室颤作用.

所以, Oxy 提高 DET 和延长 ERP 是其抗心律失常作用机制.

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左旋千金藤立定对溴隐亭诱导的哺乳期大鼠促乳素水平低下的拮抗作用

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R 966

Antagonism of *l*-stepholidine against bromocriptine-inhibition on prolactin level in lactational rats

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KEY WORDS *l*-stepholidine; bromocriptine; prolactin; dopamine D₂ receptors; lactation

AIM: To study the antagonism of *l*-stepholidine (SPD) against bromocriptine (Bro)-inhibition on prolactin (PRL) level. **METHODS:** Bro (0.5 mg · kg⁻¹ · d⁻¹, sc) reduced the PRL and caused a dysplasia of mammary gland in lactational rats. The weight growing of newborn rats was retarded. The PRL of the lactational rats was assessed by immunoradiometric assay (IRMA); the weight of newborn rats and development of mammary glands in lactational rats were also examined. Antagonism of SPD was evaluated. **RESULTS:** SPD (30 & 100 mg · kg⁻¹ · d⁻¹, ip) obviously antagonized the Bro that induced lowering the PRL level in lactational rats, the PRL was 11 ± 4 & 23 ± 6 μg · L⁻¹ (NS 7 ± 2) respectively on d 15 of postpartum and the development of mammary

gland in lactational rats was normal. The newborn rats grew rapidly in 11 - 15 d. **CONCLUSION:** SPD possessed an antagonism with Bro inhibition on D₂ receptors located in the pituitary gland, and was an antagonist of dopamine D₂ receptors.

关键词 左旋千金藤立定; 溴隐亭; 促乳素; 多巴胺 D₂ 受体; 泌乳

目的: 研究左旋千金藤立定 (SPD) 对溴隐亭 (Bro) 诱导的促乳素 (PRL) 水平低下的对抗作用
方法: 哺乳期母鼠 sc Bro 0.5 mg · kg⁻¹ · d⁻¹, PRL 显著降低, 乳腺组织发育不良, 而且仔鼠体重增长缓慢. 用放免法测定母鼠 PRL, 检查乳腺发育状况, 评价 SPD 的对抗作用. **结果:** SPD 30 及 100 mg · kg⁻¹ · d⁻¹ ip, 能够显著对抗 Bro 诱导的母鼠 PRL 降低, 分娩后 d 15 PRL 为 11 ± 4 及 23 ± 6 μg · L⁻¹ (生理盐水为 7 ± 2), 而且乳腺组织发育正常, 仔鼠在出生后 d 11 - 15 内迅速生长发育. **结论:** SPD 能阻断大鼠脑垂体前叶的 D₂ 受体, 是一个 D₂ 受体的拮抗剂.

左旋千金藤立定 (*l*-stepholidine, SPD) 是从云南河谷地不容 (*Stephania intermedia* Lo) 中分离获得的生物碱^[1], 是多巴胺受体拮抗剂^[2-5]. 脑垂体前叶促乳素分泌细胞上只存在 D₂ 受体, 抑制性调节促乳素 (Prolactin, PRL) 的分泌作用, 测定血清 PRL 是衡量脑内 D₂ 受体功能的良好指标^[6-8]. 为了论证 SPD 对 D₂ 受体的作用, 本文