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洛美沙星在10名健康志愿者体内的药物动力学及相对生物利用度

(16)

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摘要 10名健康中国男性志愿者单剂量随机交叉服用400mg洛美沙星片剂及胶囊后, 利用HPLC测得血浆中药物浓度分别在1.3±0.4和1.2±0.4h达到峰值6.0±1.3和5.9±1.0 μg·ml⁻¹. 血药曲线下面积分别为43±15和44±13 h·μg·ml⁻¹, 药-时曲线符合一级吸收的单室模型. 片剂与胶囊的各药动学参数无显著性差异, 二者生物利用度相同.

关键词 洛美沙星; 片剂; 胶囊; 药物动力学; 生物利用度

药代动力学

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(17)

哇巴因和葡萄糖酸钙联合诱发猫心脏触发性活动

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Triggered activities in cat heart induced by combined administration of ouabain and calcium gluconate

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ABSTRACT The pharmacological effects of iv a mixture of ouabain (Oua) (50 μg·kg⁻¹) and calcium gluconate (Ca²⁺) (100 mg·kg⁻¹) on the electric activities of the cat hearts (n=19) were studied by using a contact electrode and a contact electrode catheter to record both epicardial and endocardial monophasic action potentials (MAP). The results showed that the 2 drugs together reduced the MAP amplitude, decreased V_{max}, and lengthened the MAP duration. Ouabain induced triggered activities, eg, early afterdepolarization, early afterhyperpolarization, delayed afterdepolarization including oscillatory afterpotentials, and triggered arrhythmias, which were enhanced by calcium gluconate. Endocardium is more sensitive than epicardium to ouabain.

KEY WORDS electrophysiology; arrhythmia; action potentials; ouabain; calcium gluconate; heart; drug combinations

摘要 用接触电极记录MAP研究哇巴因和葡萄糖酸钙合并用药和单独用Oua对猫在体心脏电活动的药理学效应. Oua和calcium gluconate (Ca²⁺)可降低MAPA, 延长MAPD, 降低V_{max}; 还可诱发EAD, EAH, DAD(包括OAP)及多种触发性心律失常, 以EAD居多, 心内膜比心外膜对Oua更敏感. 单独用Oua触发性活动的诱发率小, 出现时间晚, Ca²⁺可促进触发性活动的产生.

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关键词 电生理学; 心律失常; 动作电位; 哇巴因; 葡萄糖酸钙; 心脏; 合并用药

洋地黄诱发的心律失常常被用作检测抗心律失常药物的模型⁽¹⁾。洋地黄类中毒可引起离体标本⁽²⁻⁴⁾的触发性活动。但整体水平上诱发比例报道不一 (Priori⁽⁵⁾ 73%, Furukawa⁽⁶⁾ 69%), 且 Ca²⁺ 是单独还是与洋地黄协同诱发, 尚有争论⁽⁵⁾。心内外膜差异方面, 未见报道。本文用心外膜接触电极⁽⁷⁾和常规心导管同步记录心内外膜单相动作电位 (monophasic action potential, MAP), 探讨洋地黄诱发的心律失常与触发性活动的关系, Ca²⁺ 的作用, 建立一稳定的触发性活动的模型, 并为临床安全使用洋地黄, 提供依据。

MATERIALS AND METHODS

家猫 25 只, ♀♂ 兼有, 体重 2.8 ± 0.6 kg, urethan 1 g · kg⁻¹ ip 麻醉, 背位固定, 正中开胸, 用自制拉钩钩制心包床, 以暴露和固定心脏, 行人工呼吸。

用心外膜接触电极引导心室外膜 MAP 输入 FL-A 高阻抗放大器; 将常规心导管 (USCI 5F) 从左颈外静脉插至右室, 单极记录右室心尖部的 MAP (参考电极在胸壁上) 输入 MEZ-8201 微电极放大器; 同时, 经 DPS-F 生理放大器引导 II 导心电图。以上 3 个放大信号都经过 HF-1 四通道后置放大器输入超级微机记忆系统 (南京医学院研制) 进行信号的记录, 测量及作图。同时, 将心内膜 MAP 和 ECG 输入 DSS 6521 记忆示波器, 以便观察。数据分析采用组间 *t* 检验。

实验共分两组, 用自动抽注机 (ZCZ-50) iv 如下试剂: 1) Oua 50 μg · kg⁻¹ 和 calcium gluconate 100 mg · kg⁻¹ 的混合液, 给药时间 5-10 min, 给药速度 (33 μg Oua + 66 mg calcium gluconate) / min, n = 19. 2) Oua 50 μg · kg⁻¹, 给药速度 (33 μg Oua) / min, n = 6. 两组均于给药前和给药后 0, 1, 3, 5, 10, 15, 20, 25, 30 min 时记录心内外膜 MAP 和 I 导 ECG。

RESULTS

Oua 和 Ca²⁺ 合并用药对猫心脏电活动的影响

1 合并用药对 MAP 的影响 合并用药使心内外膜 MAP 振幅 (MAPA) 明显降低, 这一结果与文献⁽⁶⁾ 报道一致。心内外膜 MAP 的 50% 间期 (MAPD₅₀) 在给药后无显著变化。心内膜 MAP 的 90% 间期 (MAPD₉₀) 在给药后显著增加, 15 min 时增至最大, 心外膜 MAPD₉₀ 无显著变化, 心内膜 MAP 0 相最大上升速率 (V_{max}) 无显著变化, 心外膜 V_{max} 显著降低。可见, 合并用药对心内膜和心外膜 MADP₉₀ 的影响有所不同 (Tab 1)。这一结果未见报道。

2 合并用药对 ECG 的影响 iv Oua 和 Ca²⁺ 后, 窦性心律, P-R 间期逐渐延长; 然后, P 波游走, 房室脱节, 房室传导阻滞, QRS 波群电位增大, P 波倒置, 变为室上性心律; iv 10 min 后, QRS 波群宽大而畸形, P 波

Tab 1. Effect of iv a mixture of ouabain (50 μg · kg⁻¹) and calcium gluconate (100 mg · kg⁻¹) on epicardial (Epi) and endocardial (End) monophasic action potentials (MAP) in cat heart. n = 19, $\bar{x} \pm s$. *P > 0.05, **P < 0.05, ***P < 0.01 vs before iv drugs. +P > 0.05, ++P < 0.05, +++P < 0.01 vs endocardium. MAPA: monophasic action potential amplitude; MAPD₅₀, MAPD₉₀: 50 or 90% monophasic action potential duration. V_{max}: maximum velocity of phase 0 of MAP.

		Before	0 min	1 min	5 min	15 min	25 min
MAPA/ mV	End	19.0 ± 4.4	14.7 ± 3.1***	15.5 ± 2.6**	11.6 ± 2.8***	10.1 ± 3.0***	7.7 ± 1.1***
	Epi	17.8 ± 3.6	12.6 ± 3.7****	11.3 ± 3.9****	10.2 ± 2.7****	9.7 ± 2.3****	7.6 ± 1.9****
MAPD ₅₀ / ms	End	198 ± 37	229 ± 53*	223 ± 55*	217 ± 40*	229 ± 45*	226 ± 29*
	Epi	163 ± 33+	194 ± 34***	188 ± 36**	185 ± 32***	199 ± 31**	199 ± 26***
MAPD ₉₀ / ms	End	236 ± 42	287 ± 57***	278 ± 66**	278 ± 65**	304 ± 51***	273 ± 48*
	Epi	225 ± 48+	244 ± 40**	256 ± 37**	244 ± 30**	249 ± 37****	252 ± 28**
V _{max} / V · s ⁻¹	End	1.1 ± 0.3	0.9 ± 0.3*	0.9 ± 0.2*	0.9 ± 0.4*	0.9 ± 0.3*	1.1 ± 0.4*
	Epi	1.6 ± 0.5***	1.3 ± 0.7**	1.1 ± 0.8**	1.1 ± 0.5***	1.3 ± 0.8**	1.0 ± 0.6****

消失, 形成室性心律, 表现为室性逸搏, 室性早搏, 单形性室速, 多形性室速, 室扑和室颤 (Fig 1). 这一变化与文献^(5,2)一致. 19只动物室速出现率100%, 30 min内死亡率16% (3/19).

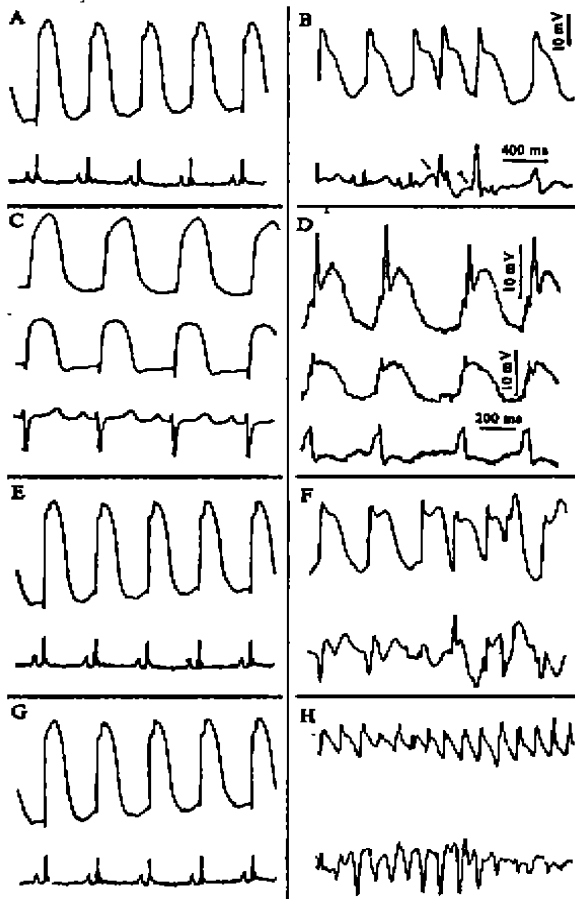


Fig 1. Ventricular arrhythmias induced by iv a mixture of ouabain ($50 \mu\text{g}\cdot\text{kg}^{-1}$) and calcium gluconate ($100 \text{mg}\cdot\text{kg}^{-1}$) in cat heart. A, C, E, and G are the controls of B, D, F, and H, respectively. B) ventricular extrasystole; D) uniform ventricular tachycardia; F) multiform ventricular tachycardia; H) ventricular flutter and fibrillation. A, B, E, F, G, H with the same criteria. C, D, with the same criteria.

3 合并用药诱发猫心脏触发性电活动
iv Oua 和 Ca 后, 13只猫5 min内在 MAP 3相中晚期产生早期后去极化(early afterdepolari-

zation, EAD, Fig 2); 2只猫在3相末产生早期后超极化(early afterhyperlarization, EAH), 并且在其后4相均伴有延迟性后去极化(delayed afterdepolarization, DAD, Fig 2), 其中1只猫在23 min时, 出现振荡性后电位(oscillatory afterpotential, OAP, Fig 2). 当 EAD 和

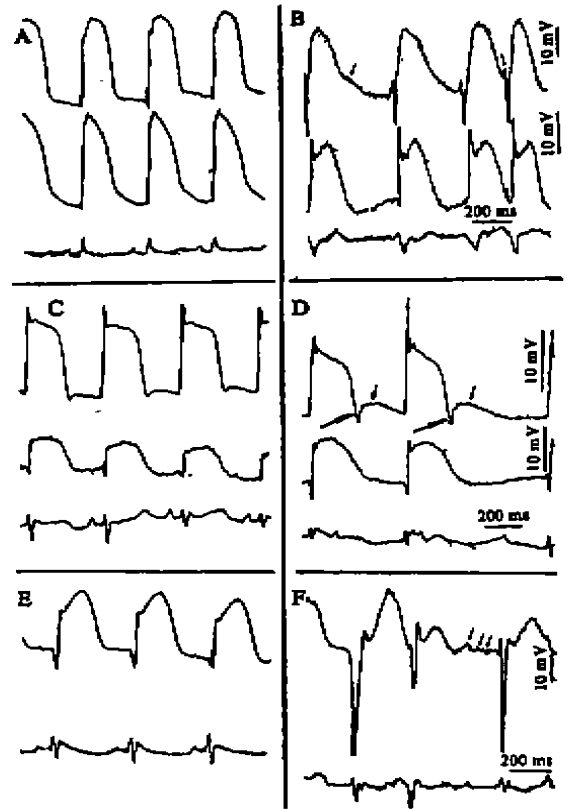


Fig 2. Afterpotentials induced by iv a mixture of ouabain ($50 \mu\text{g}\cdot\text{kg}^{-1}$) and calcium gluconate ($100 \text{mg}\cdot\text{kg}^{-1}$) in cat heart. A, C, and E are the controls of B, D, and F, respectively. B shows the EAD and triggered extrasystole. D shows the DAD (\uparrow) and EAH (\uparrow). F shows OAP. Upper tracing) endocardial MAP; middle tracing) epicardial MAP; lower tracing) lead I of ECG.

DAD 达到阈值时, 可以触发多种心律失常 (Fig 1). 根据心律失常与后电位的关系, 可以分为三类: 1) 室早或室速的第一个 MAP 发生于前一 MAP 的后电位上或十分接近于前一 MAP

的后电位, 室早的耦联间期(coupling interval, CI)与后电位的 CI 基本相同 $CI_{\text{早}} = 1.28 CI_{\text{后电位}} - 14.75$, $n = 14$, $r = 0.97$; 2) 室早或室速的第一个 MAP 并非发生于前一 MAP 的后电位上, 前者的 CI (406 ± 63 ms) 显著大于后者的 CI (281 ± 33 ms), $P < 0.01$, $n = 23$; 3) 未记录到后电位, 但有室性心律失常出现. 另外, 后电位在心内膜 MAP 上的出现率 15/19 远大于心外膜上的出现率 2/19.

单独用 Oua 对猫心脏电活动的影响 猫 6 只有 3 只记录到 EAD (50%), 1 只记录到 DAD (16.7%). 后电位多在 iv 后 10-20 min 内出现, iv 10 min 后, 心律由窦性变为结性, 室性. 与合并用药比较可以看出: 后电位总的诱发率下降, 触发性活动出现的时间推迟.

DISCUSSION

实验表明, 合并用药所引起的室性心律失常的机制分为两类: 一类产生于后去极化上的室性心律失常可以肯定是触发机制引起的; 另一类可能是由非记录部位的后电位触发产生, 或由其它机制引起的.

本文首次发现, Oua 主要诱发 EAD 而非 DAD, 与文献^(2-5,9)不一致. 可能的原因是在体心脏上药物除直接作用于心脏外, 还作用于神经系统而间接作用于心脏. Oua 可兴奋迷走抑制交感使心率减慢, MAPD 延长⁽⁸⁾. EAD 具有慢频率依赖性, DAD 具有快频率依赖性⁽¹¹⁾. 所以, 在体心脏更易诱发 EAD.

浦氏纤维比心室肌细胞对洋地黄类药物更敏感^(9-10,12). 由于浦氏纤维主要分布于心内膜, 所以心内膜 MAPD₉₀ 变化更大, 记录到的后电位比例更大.

Iv Ca^{2+} 与 Oua 协同作用, 加强触发性活动. 提示 Oua 通过调节细胞内 $[Ca^{2+}]_i$ 的变化⁽⁸⁾而诱发触发性活动的.

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