

并不能增加哌嗪二酮母体结构进入血脑屏障。由此推测当肿瘤转移到脑或脊髓后, probimane 可能无效。

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(22)

BIBLID: ISSN 0253-9756 中国药理学报 *Acta Pharmacologica Sinica* 1993 Mar; 14 (2) : 173-175

蝙蝠葛碱的首次通过效应

R 965.2

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First-pass effect of dauricine

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ABSTRACT The first-pass effect of dauricine (Dau) was compared with that of lidocaine (Lid) by measuring the ventricular fibrillation threshold (VFT) and dauricine plasma concentration in rats or rabbits.

After forelimb or mesenteric vein (imv) infusion of Dau at a rate of 1 mg · kg⁻¹ · min⁻¹ in rats, the VFT were 1.64-3.17 or 1.60-2.11 V, respectively. In the case of Lid at 2.5 mg · kg⁻¹ · min⁻¹, the VFT were 1.69-4.79 or 1.67-2.80 V, respectively, after ear vein (iev) or imv infusion of Dau at a rate of 0.5 mg · kg⁻¹ · min⁻¹ in rabbits, the VFT were 6.50-12.14 or 5.81-7.43 V, respectively. Plasma Dau concentration through iev infusion was significantly higher than that through imv route. As the dose of imv infusion increased, AUC of Dau showed a nonlinear increase.

The results suggested that Dau showed a considerable first-pass effect, which was dose-dependent.

Received 1990-10-10 Accepted 1992-09-09

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KEY WORDS dauricine; lidocaine; pharmacokinetics; ventricular fibrillation

摘要 大鼠、兔门静脉系统、体静脉系统两种途径给药, 以给药后左心室电致颤阈(VFT)或药物的血浆浓度为指标, 研究蝙蝠葛碱(Dau)、利多卡因(Lid)的首次通过效应。结果 Dau 与 Lid 一样存在明显首过效应, 且表现为剂量依赖性。

关键词 蝙蝠葛碱; 利多卡因; 药物动力学; 心室纤颤

在氟仿所致小鼠室颤模型, 蝙蝠葛碱(dauricine, Dau) ig 的 ED_{50} 为 iv 的 12 倍, 小鼠 ig LD_{50} 为 iv 的 17 倍, 大鼠则为 92 倍^[1]。以上结果均表明 Dau 胃肠道吸收不全或类似利多卡因(lidocaine, Lid)存在明显首过效应^[2]。本实验拟以大鼠、兔给药后左心室电致颤阈(ventricular fibrillation threshold, VFT)及药物血浆浓度为指标, 研究 Dau 首过效应及影响因素。

肠系膜静脉给药, 药物经肝脏摄取处置后再进入体循环, 这是与体静脉直接给药唯一不同之处, 故本实验旨在研究 Dau 的肝脏首过效应。

MATERIALS AND METHODS

Dau 粉剂(同济医科大学药学系植化室精制), 纯度 97%, Lid 注射液(上海第十三制药厂), 层析硅胶板(15×15 cm GF₂₅₄, 国营浙江黄岩化学实验厂), 双波长薄层扫描仪(日本岛津 CS-930)。

大鼠、兔均由同济医科大学实验动物中心提供。

Dau, Lid 前肢静脉、肠系膜静脉给药对大鼠 VFT 的影响 SD 大鼠 32 只, ♂, 体重 $220 \pm s 37$ g, ip 3%戊巴比妥钠 $30 \text{ mg} \cdot \text{kg}^{-1}$ 。麻醉后人工呼吸下开胸, 方波刺激器正极夹于心尖部, 负极夹于左室心外膜, 两极相距 5 mm, 施以波宽 0.5 ms, 频率为 50 Hz 的电刺激, 在 15 s 内连续递增电压, 求得 VFT^[3]。

四组大鼠分别肠系膜静脉或前肢静脉恒速灌注 Lid $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ 或 Dau $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, 分别于给药后 30 min 内每 5 min 测定 VFT 一次, 以

比较两种给药途径在相同剂量下 VFT 的差。

Dau 耳缘静脉、肠系膜静脉给药对兔 VFT 及药物血浆浓度的影响 日本大耳白兔 21 只, ♂ ♀ 不拘, 体重 1.97 ± 0.25 kg, 分为四组, iv 3%戊巴比妥钠 $30 \text{ mg} \cdot \text{kg}^{-1}$ 。麻醉后开胸, 暴露心脏, 切开心包膜但不损伤胸膜以保持自主呼吸, 方波刺激器正极夹于心尖部, 负极夹于左室心外膜, 两极相距 10–15 mm, 施以波宽 1 ms, 频率 50 Hz 的电刺激, 每次持续 5 s, 每隔 3 min 刺激一次, 逐次提高电压 0.5–1.0 V 求得 VFT^[4]。

一组耳缘静脉恒速灌注 Dau $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, 其它三组分别肠系膜静脉恒速灌注 Dau 0.5, 1.5, 3.0 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ 。于给药后 5, 15, 25 min 测定 VFT, 同时颈动脉取血, 以薄层荧光扫描法^[5]测定血浆中 Dau 浓度, 以比较两种不同途径给药对 VFT 的影响及血浆浓度差异。

RESULTS

Lid $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, Dau $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ 分别前肢静脉、肠系膜静脉恒速灌注对大鼠 VFT 的影响见 Tab 1。结果显示, 给药后各相同时间点, 前肢静脉给药组的 VFT 均显著高于肠系膜静脉给药组。

Dau $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ 分别耳缘静脉、肠系膜静脉恒速灌注, 兔 VFT 及血浆浓度分别见 Tab 2, Tab 3。结果表明, 给药后各相同时间点, 相同剂量下耳缘静脉给药组的 VFT 及血浆浓度均显著高于肠系膜静脉给药组。3 倍于耳缘静脉给药组的剂量($1.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)肠系膜静脉灌注, 其 VFT 在给药后各时间点与耳缘静脉给药组无显著性差异, 其血浆浓度在给药后 5, 15 min 与耳缘静脉给药组无显著性差异。6 倍于耳缘静脉给药组的剂量($3.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)肠系膜静脉灌注, 其血浆浓度在给药后 15, 25 min 均显著高于耳缘静脉给药组。以梯形法计算肠系膜静脉给药后 5–25 min 的曲线下面积(AUC), 随着剂量的增加 AUC 显著增加, 当剂量增加 3 倍时 AUC 增加 4.7 倍, 当剂量增加 6 倍时 AUC 增加 12.6 倍。故剂量与 AUC 间非直线相关。

Tab 1. Effect of dauricine (Dau) and lidocaine (Lid) via mesenteric vein (imv) or forelimb vein (ifv) infusion on ventricular fibrillation threshold induced electrically in rats. $n=8$, $\bar{x} \pm s$. * $P > 0.05$, ** $P < 0.05$, * $P < 0.01$ vs imv.**

Drug / mg · kg ⁻¹		Ventricular fibrillation threshold / V	
		imv	ifv
Lid	0	1.67 ± 0.33	1.69 ± 0.53 *
	12.5	1.67 ± 0.33	2.29 ± 0.73***
	25	1.81 ± 0.44	2.76 ± 0.74***
	37.5	1.89 ± 0.41	3.23 ± 0.57***
	50	2.19 ± 0.48	3.87 ± 0.80***
	62.5	2.59 ± 0.62	4.50 ± 1.10***
	75	2.80 ± 0.52	4.79 ± 1.10***
Dau	0	1.60 ± 0.16	1.64 ± 0.21 *
	5	1.60 ± 0.16	1.81 ± 0.18**
	10	1.60 ± 0.16	2.01 ± 0.23***
	15	1.66 ± 0.13	2.39 ± 0.38***
	20	1.74 ± 0.18	2.54 ± 0.31***
	25	1.95 ± 0.28	2.96 ± 0.37***
	30	2.11 ± 0.41	3.17 ± 0.35***

Tab 2. Effects of dauricine via ear vein (iev) or mesenteric vein (imv) infusion on ventricular fibrillation threshold (VFT) induced electrically in rabbits. $n=6$, $\bar{x} \pm s$. * $P > 0.05$, ** $P < 0.05$, * $P < 0.01$ vs iev.**

Time / min	Ventricular fibrillation threshold / V		
	iev	imv	1.5 / mg · kg ⁻¹ · min ⁻¹
0	5.85 ± 1.25	5.81 ± 1.07 *	5.70 ± 1.17 *
5	6.50 ± 1.61	5.81 ± 1.07**	6.61 ± 1.06 *
15	9.14 ± 1.57	6.18 ± 1.13***	8.95 ± 1.12 *
25	12.14 ± 1.49	7.43 ± 1.40***	11.95 ± 1.49 *

Tab 3. Dauricine concentration in plasma after ear vein (iev) or mesenteric vein (imv) infusion in rabbits. $\bar{x} \pm s$. * $P > 0.05$, ** $P < 0.05$, * $P < 0.01$ vs iev.**

	Dose / mg · kg ⁻¹ · min ⁻¹	n	Concentration of dauricine / ng · ml ⁻¹		
			5 min	15 min	25 min
iev	0.5	6	855 ± 515	1 036 ± 565	1 341 ± 433
imv	0.5	6	91 ± 24***	145 ± 41***	181 ± 57***
	1.5	6	459 ± 80 *	662 ± 231 *	858 ± 224**
	3.0	3	1 030 ± 448 *	1 826 ± 125**	2 303 ± 121***

DISCUSSION

Lid 给大鼠系膜静脉灌注与体静脉给药的 VFT 在给药后各时间点均有显著性差异, 其比值分别在 0.58-0.72 之间. 此结果表明, 以 VFT 为观察指标定性研究抗心律失常药物的首过消除效应是可行的, 但不能作为定量研究的指标.

Dau 在大鼠两种途径给药后相同时间点的 VFT 均有显著差异, 以免为实验对象获同样的结果, 表明 Dau 与 Lid 一样有明显首过效应.

Dau 两种不同途径给药后, 在相同剂量下, 体静脉给药组的血浆浓度显著高于肠系膜静脉给药组, 增加肠系膜静脉灌注剂量, AUC 呈非线性增加, 此结果表明肝脏对 Dau 的摄取呈剂量依赖性.

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