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赛拉唑对清醒犬心率和血压的影响

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Effects of xylazole on heart rate and blood pressure in conscious dogs

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ABSTRACT Xylazole (Xyl) is an analogue of xylazine (Xyn) synthesized by Lanzhou Institute of Chinese Traditional Veterinary Medicine. The effects of Xyl on heart rate and blood pressure were studied in 5 conscious dogs. Xyl 1 mg/kg iv was similar to Xyn in producing bradycardia and an initial transient hypertension followed by a lasting hypotension which was less significant than Xyn. Yohimbine (0.1 and 0.3 mg/kg), an α_2-adrenoreceptor blocking agent, antagonized bradycardia and hypotension induced by Xyl. Tolazoline (3.3 mg/kg), a nonselective α-adrenoreceptor blocking agent, reversed the bradycardia and hypotensive effect. Prazosin (1 mg/kg),

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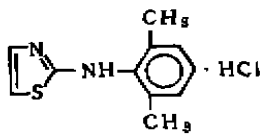
an α_1-adrenoreceptor blocking agent, did not change Xyl-induced *bradycardia and* hypotension. Atropine (20 μg/kg) not only antagonized Xyl-induced bradycardia but also changed from bradycardia to tachycardia, and greatly potentiated Xyl-induced hypertension for more than 30 min. The results suggested that Xyl-induced cardiovascular effects are similar to Xyn that mediated by α_2-adrenoreceptor.

KEY WORDS xylazole; xylazine; yohimbine; atropine; heart rate; blood pressure; adrenergic alpha receptor blockaders

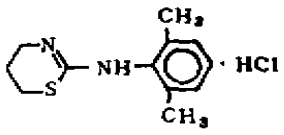
摘要 清醒犬 iv 赛拉唑 1 mg/kg 呈现与赛拉嗪类似的先升压后降压和心率减慢的作用。α_2 受体阻滞剂育享宾和 α_1，α_2 受体阻滞剂妥拉唑林均能拮抗这种作用，而 α_1 受体阻滞剂哌唑嗪无此作用。阿托品 iv 不仅拮抗其减慢心率作用，而且反而大大加速心率，强烈升高血压。赛拉唑对心血管的影响似与 α_2 受体有关。

关键词 赛拉唑；赛拉嗪；育享宾；阿托品；心率；血压；肾上腺素 α 受体阻滞剂

赛拉唑(xylazole, Xyl)是兰州中国农科院中兽医研究所合成的一种赛拉嗪(xylazine, Xyn)类似物，化学名为盐酸2-(2,6-二甲基苯胺基)-5,6-二氢-4H-1,3-噻唑(2-(2,6-dimethylanilino)-5,6-dihydro-4 H-1,3-thiazole hydrochloride)，有良好的镇静、镇痛和肌松弛作用，而毒性则较小[1]。Xyn 是一个 α_2 受体激动剂[2]，与戊巴比妥钠配合用于犬的麻醉不仅可减少巴比妥的药量，而且其麻醉过程随时可被育享宾(yohimbine, Yoh)所中断而催醒[3,4]，但它有先升压后降压和减慢心率的不良影响[5~7]。本文是在清醒犬上观察 Xyl 是否有与 Xyn 相类似的心血管效应，并且这种作用能否被不同的 α 受体阻滞剂 Yoh、哌唑嗪和妥拉唑林或胆碱能阻滞剂阿托品所拮抗，并分析其性质。



Xylazole



Xylazine

MATERIALS AND METHODS

药物 Xyl，由兰州中兽医研究所化学合成室提供；Xyn，美国 Bayvet 药厂；Yoh、阿托品、妥拉唑林，美国 Sigma 公司；哌唑嗪，美国 Pfizer 药厂。除 Xyl 和哌唑嗪溶于 3% 乳酸外，余均溶于蒸馏水。

实验犬的制备 5 只♂犬(其中 3 只为 beagle 种犬，2 只为杂种犬)，体重 12.4±SD 2.6 kg，均经手术[8]制成慢性股动、静脉导管瘘，并在四腿皮下埋植不锈钢电板，供记录心电图用。术后 1 wk 再开始做实验。

血压和心率的测定 清醒犬每次在测定动脉压(BP)和心率(HR)前先停食 14-18 h。在正常清醒状态下放在实验小室 (1×1×2 m) 内安静 1 h，室温 18-20℃。股静脉输药。动脉导管连接压力换能器测股动脉 BP，用 EKG 第 11 导程连接皮肤上的不锈钢电板，记录 HR，均用 Beckman R 611 多道仪持续记录 BP 和 HR。

Xyl 和 Xyn 各 1 mg/kg 均在 0 h iv，对照犬在 0 h iv 0.9% NaCl；各种阻滞剂：Yoh 0.1，0.3 mg/kg，哌唑嗪 1 mg/kg，妥拉唑林 3.3 mg/kg 和阿托品 20 μg/kg 均在 iv Xyl 后 5 min iv，观察 5，10，20，40，60，90 和 120 min 时的 BP 和 HR 变化(阿托品增加一个 15 min 的数据)，进行比较。用随机区组设计。所有各犬除进行 Xyl，Xyn 和对照 3 次试验外，均还进行以上 4 种阻滞剂的 5 次拮抗试验，但为了减少前药的残余影响，两次试验的间隔时间至少 6 d。组间显著性比较采用两因子方差分析。

RESULTS

Xyl 和 Xyn 对 BP 和 HR 的影响 对照犬 iv 0.9%NaCl 后 BP 和 HR 在整个 120 min 内没有明显变化($P>0.05$)。iv Xyn 1 mg/kg 后出现典型的先升压后降压和伴有心律失常和停搏的 HR 减慢作用。其升压作用与对照犬 5 min 时和 0 h BP 相比相差显著，其降压作用仅在

40 min 时与对照犬 BP 相比差异显著。HR 减慢变化在 120 min 内均显著 ($P<0.05$, 0.01) (Fig 1)。Xyl 对 BP 和 HR 的影响与 Xyn 基本相似($P>0.05$)，只是升压幅度大于 Xyn，降压速度比 Xyn 略慢，幅度也较小；HR 减慢非常显著($P<0.01$)，但其幅度与 Xyn 相比差异不显著(Fig 1)。两药 iv 后 1-2 min 内犬均处于静卧状态，嗜睡，有 2/5 犬出现呕吐。

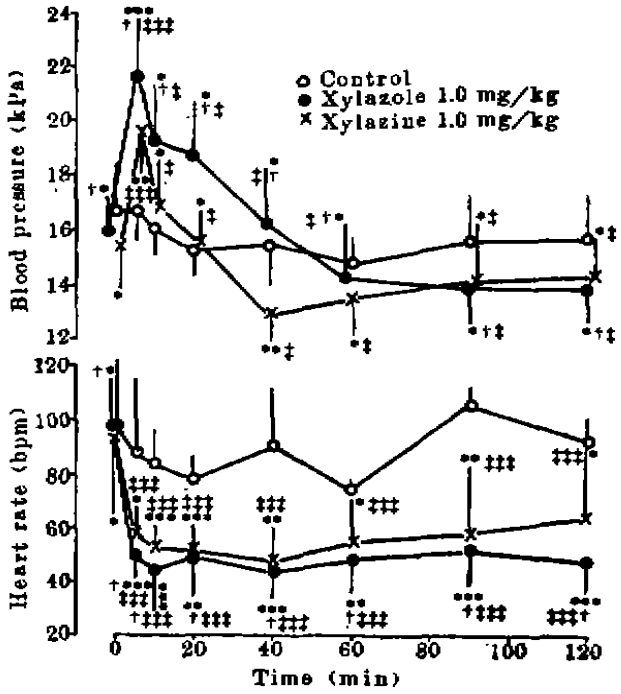


Fig 1. Arterial blood pressure and heart rate changes after administration of xylazole or xylazine. Both drugs were given iv at 0 time. $n=5$, $\bar{x}\pm SD$. *$P>0.05$, **$P<0.05$, ***$P<0.01$ *vs* control; †$P>0.05$, ††$P<0.05$, †††$P<0.01$ *vs* xylazine; ‡$P>0.05$, ‡‡$P<0.05$, ‡‡‡$P<0.01$ *vs* 0 time.

Yoh 对 Xyl 作用的影响 用 Xyl 处理过的犬在 iv Yoh 0.1, 0.3 mg/kg 后，减慢的 HR 逐渐加快，升高的 BP 慢慢下降，从 20 min 开始 HR 和 BP 与对照犬在统计上已无显著差异 (Tab 1)。较大剂量的 Yoh 拮抗 Xyl 的作用略强于小剂量 Yoh，但无统计意义。在 Yoh 作用下，犬在短时内即由睡卧状态转为清醒，有流涎、肌肉颤抖和窦性心律失常消失。

哌唑嗪和妥拉唑林对 Xyl 作用的影响 iv 哌唑嗪 1.0 mg/kg 对 Xyl 引起的减慢 HR 和升降 BP 的作用不显著，但妥拉唑林 3.3 mg/kg 则能拮抗 Xyl 减慢 HR 的作用，特别是在 40 min 以后($P<0.05$)(Tab 1)。妥拉唑林有轻度拮抗 Xyl 的镇静作用。

阿托品对 Xyl 作用的影响 在给于 Xyl 后 5 min iv 阿托品 20 μg/kg，BP 在升高的(22.3 ±SD 1.6 kPa，167 ±SD 6 mmHg) 基础上急剧上升，15 min 时高达 32±3 kPa (237±12 mmHg)，维持 10 min，然后缓慢下降，到 60 min 左右才接近于正常；HR 在给阿托品后 5 min 由心动徐缓转变为心动过速，15 min 时最高达 167±34 bpm，约在 60 min 时回复到正常，进而又略慢于正常(Tab 1)。由于心动过速，心电图上出现频繁的 II 度房室传导阻滞和室性心律失常。犬呼吸急促，显现高度不适、疲乏，卧伏在地，不能动弹。

DISCUSSION

从以上特异性 α_2 受体阻滞剂 Yoh 对 Xyl 心血管系统作用的影响看，Xyl 与 Xyn[5-7] 一样，也是 α_2 受体激动剂。其升压作用可能是激活小动脉血管床的 α 受体，包括突触后 α_2 受体[5,9]，引起血管收缩，外周阻力增加。而其降压和减慢 HR 作用则可能是由于：1)有使压力感受性反射易化的作用，增强迷走神经的紧张度[5,11]，减慢 HR 和产生房室传导阻滞；2)抑制心肌收缩力，减少输出量[10]；3)作用于中枢脑桥延髓区的突触前和突触后 α_2 受体，减少去甲肾上腺素的释放[5,10]；4)激活肾上腺素能神经末端的突触前 α_2 受体而抑制其周围神经递质的释放[5,9]。

特异性 α_1 受体阻滞剂哌唑嗪不能拮抗 Xyl 引起的升压、降压和减慢 HR 的作用，而 α_1，α_2 受体阻滞剂妥拉唑林则能拮抗其减慢 HR 的作用，这也正说明上述 Xyl 的作用与 α_2 受体有关。

给 Xyl 后 iv 阿托品所引起的 BP 急剧升高

Tab 1. Effects of yohimbine (Yoh), prazosin (Pra), tolazoline (Tol) or atropine (Atr) on xylazole (Xyl)-induced mean blood pressure (BP, kPa) and heart rate (HR, bpm) in conscious dogs. Xyl was given iv at 0 time, and potential antagonists were given iv at 5 min. $n=5$, $\bar{x}\pm SD$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* xylazole; $^{\dagger}P>0.05$, $^{\dagger\dagger}P<0.05$, $^{\dagger\dagger\dagger}P<0.01$ *vs* control.

Drug	(mg/kg)		0	5	10	20	40	60	90	120 min
Control		BP	16.8±1.6	16.7±1.1	16.1±0.9	15.3±0.9	15.5±1.5	14.8±0.9	15.6±1.6	15.7±1.5
		HR	98±24	88±27	84±12	78±8	90±21	74±2	104±7	92±8
Xyl	1	BP	16±1.2 †	21.7±2.1 ††*	19.3±2.1 †	18.7±1.9 †	16.3±1.9 †	14.3±1.9 †	13.9±1.4 †	13.9±1.3 †
		HR	98±17 †	49±7 †††	45±16 †††	49±14 ††	44±10 †††	48±12 ††	51±13 †††	46±10 †††
Yoh	0.1	BP	15.3±0.8 *†	22.3±2.1 *††	21.3±1.3 *†††	16.3±1.0 *†	14.5±1.2 *†	13.9±1.2 *†	15.5±0.9 *†	16±1.4 *†
		HR	88±19 *†	38±2 *†††	42±10 *†††	55±18 *†	58±21 *††	66±12 *†	70±11 *††	77±15 **†
	0.3	BP	15.7±0.6 *†	22.3±1.2 *†††	21.6±1.4 *†††	16.5±2.2 *†	17.1±3.5 *†	16.5±2.7 *†	16.8±2.9 *†	16.4±2.5 *†
		HR	91±10 *†	49±20 *†††	50±12 *†††	77±15 *†	74±21 **†	89±27 ***†	97±25 ***†	88±24 ***†
Pra	1	BP	14.8±1.5 *†	22.5±3.0 *†††	21.3±2.5 *†††	16.4±0.8 *†	15.1±1.0 *†	15.9±2.8 *†	16.3±3.4 *†	16.4±2.3 *†
		HR	87±18 *†	39±9 *†††	40±6 *†††	42±8 *††	42±4 *†††	46±7 *††	45±9 *†††	47±14 *†††
Tol	3.3	BP	15.3±2.3 *†	23.9±4.0 *†††	21.5±3.1 *†††	16.3±1.2 *†	14.8±2.4 *†	15.7±1.9 *†	17.1±2.5 *†	16.9±1.9 *†
		HR	88±17 *†	45±6 *†††	52±17 *†††	56±9 *†	73±20 **†	80±22 **†	82±21 *†	73±21 *†
Atr	0.02	BP	15.3±1.1 *†	22.3±1.6 *†††	21.3±1.3 *†††	31.7±3.2 ***†††	23.9±4.4 ***†††	17.7±3.0 *†	16.1±1.9 *†	15.7±1.5 *†
		HR	92±12 *†	42±9 *†††	44±7 *†††	152±24 ***†††	97±19 ***†	74±21 *†	61±13 *†††	61±13 *†

和强烈的心动过速均表明在消除心脏迷走神经的减压反射后，充分显现出了 Xyl 收缩小动脉的作用，在升高 BP 的同时，也能增高心脏对肾上腺素的敏感性[10]，以致 HR 远高于正常水平。阿托品这种强烈地升高 BP 和加速 HR 的作用，用它来拮抗 Xyl 减慢 HR 的不良反应似并不安全。

由此可见，Xyl 对心血管的效应非常复杂，对血管既有收缩也有扩张的成分，对心脏既有增强迷走神经紧张度的作用又有提高对肾上腺素敏感性的作用。

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水飞蓟宾对猪脑基底动脉 5-脂氧酶活性的抑制作用[1]

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Inhibitory effect of silybin on the activity of 5-lipoxygenase of the porcine cerebral basilar artery

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ABSTRACT The chopped porcine cerebral basilar arteries (PCBA) were incubated in the modifed Tyrode solution with calcium ionophore calcimycin (A-23187, Cal) 10 μmol/L in the presence of arachidonic acid 30.6 μmol/L and indomethacin, a cyclooxygenase inhibitor 2.8 μmol/L. The culture was extracted and purified with a SEP-PAK column (SEP-PAK C_{18} Cartridge, Waters). The bioassay of the extract was then made on the isolated guinea pig ileum with the standard leukotriene D_4 (LTD_4) 200 pg/ml as a reference. The acetylcholine, histamine and 5-HT released by the ileum was preblocked by atropine 1 μmol/L, diphenhydramine 1 μmol/L and cyproheptadine 3 nmol/L. The contraction produced by the extract on the ileum showed the same characterestic as LTD_4, and was blocked by the specific LTs antagonist FPL 55712 100 ng/ml. Reversed phase high performance liquid chromatography analysis indicated the presence of peaks co-chromatographing with standard LTB_4, C_4 and D_4. The retention times of LTB_4, C_4 and D_4 in our system were 2.2, 3.2, 5.5 min respectively. The eluates of peaks co-chromatographing with LTB_4, C_4 and D_4 were collected and tested for contractile activity on the guinea pig iluem. Only the substances which had the similar LTC_4 and LTD_4 retention times exhibited contractile activities. Hence we concluded that the substances of LTs which had biological activities

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